(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
13 May 2004 (13.05.2004)

PCT

(10) International Publication Number
WO 2004/039762 A1

(51) International Patent Classification[7]: C07C 217/10, 275/32, 311/29, C07D 263/22, 413/04, A61K 31/137, A61P 11/00

(21) International Application Number:
PCT/EP2003/012194

(22) International Filing Date: 30 October 2003 (30.10.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0225535.4 1 November 2002 (01.11.2002) GB

(71) Applicant *(for all designated States except US)*: **GLAXO GROUP LIMITED** [GB/GB]; Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN (GB).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **GUNTRIP, Stephen, Barry** [GB/GB]; GlaxoSmithKline, Gunnels Wood Road, Stevenage, Hertfordshire SG1 2NY (GB).

(74) Agent: **FLORENCE, Julia, Anne**; GlaxoSmithKline, Corporate Intellectual Property (CN925.1), 980 Great West Road, Brentford, Middlesex TW8 9GS (GB).

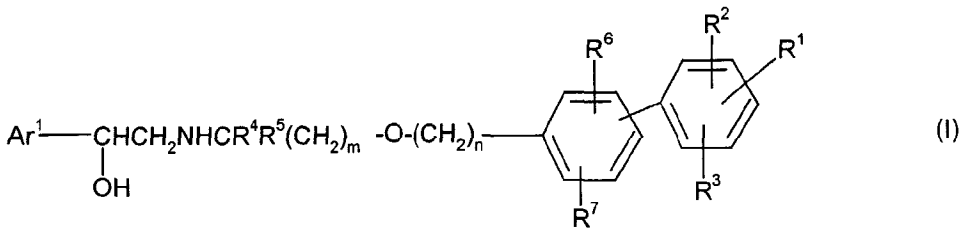
(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PHENETHANOLAMINE DERIVATIVES FOR THE TREATMENT OF RESPIRATORY DISEASES



(I)

(57) Abstract: The present invention relates to novel compounds of formula (I), to a process for their manufacture, to pharmaceutical compositions containing them, and to their use in therapy, in particular their use in the prophylaxis and treatment of respiratory diseases.

WO 2004/039762 A1

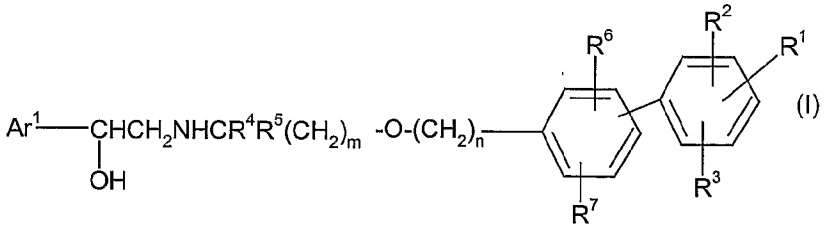
PHENETHANOLAMINE DERIVATIVES FOR THE TREATMENT OF RESPIRATORY DISEASES

The present invention is concerned with phenethanolamine derivatives, processes for their preparation, compositions containing them and their use in medicine, particularly in the prophylaxis and treatment of respiratory diseases.

Certain phenethanolamine compounds are known in the art as having selective stimulant action at β_2-adrenoreceptors and therefore having utility in the treatment of bronchial asthma and related disorders. Thus GB 2 140 800 describes phenethanolamine compounds including 4-hydroxy-α^1-[[[6-(4-phenylbutoxy)hexyl]amino]methyl]-1,3-benzenedimethanol 1-hydroxy-2-naphthalenecarboxylate (salmeterol xinafoate) which is now used clinically in the treatment of such medical conditions.

Although salmeterol and the other commercially available β_2-adrenoreceptor agonists are effective bronchodilators, the duration of action is approximately 12 hours, hence twice daily dosing is often required. There is therefore a clinical need for compounds having potent and selective stimulant action at β_2-adrenoreceptors and having an advantageous profile of action.

According to the present invention, there is provided a compound of formula (I)



or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 3 to 7;
with the proviso that m + n is 5 to 12;

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8C(O)NC(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or $-XC(O)NR^9R^{10}$;

or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, nitro, $CONR^9R^{10}$, $-NR^8C(O)R^9$, SR^8, SOR^8, $-SO_2R^8$, $-SO_2NR^9R^{10}$, $-CO_2R^{10}$, $-NR^9R^{10}$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6, preferably 0 to 4;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^8 and R^9 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl, C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, $-NHC(O)(C_{1-6}$alkyl), $-SO_2(C_{1-6}$alkyl), $-SO_2$(aryl), $-CO_2H$, and $-CO_2(C_{1-4}$alkyl), $-NH_2$, $-NH(C_{1-6}$alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, $-NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), $-NHSO_2$hetaryl, $-NHSO_2(C_{1-6}$alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or where R^1 is $-XNR^8C(O)NR^9R^{10}$, R^8 and R^9 may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an imidazolidine ring, such as imidazolidine-2,4-dione;

or where R^1 is $-XNR^8C(O)OR^9$, R^8 and R^9 may, together with the -NC(O)O- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring, preferably a 5-, 6-, or 7- membered ring, for example an oxazolidine ring, such as oxazolidine-2,4-dione;

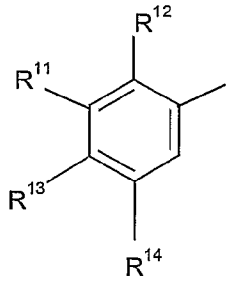
R^{10} is selected from hydrogen, C_{1-6}alkyl and C_{3-7} cycloalkyl;

or where R^1 contains a moiety $-NR^9R^{10}$ or R^9 and R^{10} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

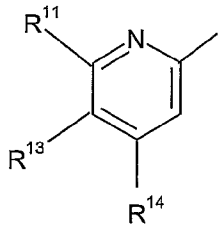
R^2, R^3, R^6, and $R^7$are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halo, and C_{1-4} haloalkyl;

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

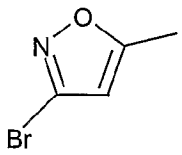
Ar^1 is a group selected from



(a)

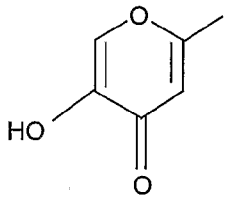


(b)



(c)

and



(d)

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_qOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,

and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}$ R^{16}, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$;

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups

$-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl, hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4.

In a particular embodiment, this invention provides a compound of formula (I) or a salt, solvate or physiologically functional derivative thereof wherein:

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8C(O)NC(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or $-XC(O)NR^9R^{10}$;

R^{11} is as defined above except that R^{11} is not hydrogen; and

all other substituents are as defined for formula (I) above.

In the compounds of formula (I) an aryl group or moiety may be for example phenyl or naphthyl.

In the compounds of formula (I) a hetaryl group may be for example pyrrolyl, furyl, thienyl, pyridinyl, pyrazinyl, pyridazinyl, imidazolyl, tetrazolyl, tetrahydrofuranyl, oxazolyl, thiazolyl or thiadiazolyl.

In the compounds of formula (I), the ring bearing the substituents R^1, R^2 and R^3 ('outer' ring) is preferably attached at the meta- or para- position of the ring bearing the substituents R^6 and R^7 ('inner' ring) relative to the $-O-(CH_2)_n-$, link. The group R^1 is preferably attached to the ortho- or meta-position of the 'outer' phenyl ring, relative to the point of attachment to the 'inner' phenyl ring.

In the compounds of formula (I) R^1 preferably represents hydroxy, $-XR^8(CO)NR^9R^{10}$, $-XSO_2NR^9R^{10}$, $-XCO_2R^{10}$, $XC(O)NR^9R^{10}$ or X-hetaryl.

R^8, R^9 and R^{10} are preferably each independently selected from hydrogen, C_{1-4}alkyl or C_{3-7}cycloalkyl.

In the definition of X, the term alkenylene includes both *cis* and *trans* structures. Examples of suitable alkenylene groups include –CH=CH-.

X is preferably $(CH_2)_r$ where r is 0 to 2, or C_2alkenylene.

In the compounds of formula (I) R^2 and R^3 preferably each represent hydrogen.

R^4 and R^5 are preferably independently selected from hydrogen and methyl, more preferably R^4 and R^5 are both hydrogen.

In the compounds of formula (I), m is suitably 3, 4, 5 or 6 and n is suitably 3, 4, 5 or 6. Preferably m is 5 and preferably n is 4 or 5, such that m + n is 9 or 10, preferably 9.

In the compounds of formula (I) the group Ar^1 is preferably selected from groups (a) and (b) above.

In said groups (a) and (b), when R^{11} represents halogen this is preferably chlorine or fluorine.

$R^{15}$and R^{16} preferably each independently represent hydrogen or methyl.

R^{17} preferably represents substituted phenyl.

The integer q preferably represents zero or 1.

Thus for example $-(CH_2)_qOR^{15}$ preferably represents OH or $-CH_2OH$;
$NR^{15}C(O)R^{16}$ preferably represents –NHC(O)H;
$-SO_2NR^{15}R^{16}$ preferably represents $-SO_2NH_2$ or SO_2NHCH_3;
$-NR^{15}SO_2R^{16}$ preferably represents $NHSO_2CH_3$;
$NR^{15}R^{16}$ preferably represents $–NH_2$;
$-OC(O)R^{17}$ preferably represents substituted benzoyloxy eg. $OC(O)-C_6H_4-(p-CH_3)$; and
$–OC(O)N\ R^{15}\ R^{16}$ preferably represents $OC(O)N(CH_3)_2$.

When R^{11} represents NHR^{18} and together with R^{12} forms a 5- or 6- membered heterocyclic ring $-NHR^{18}-R^{12}-$ preferably represents a group:

$-NH-CO-R^{19}-$ where R^{19} is an alkyl, alkenyl or alkyloxy group;

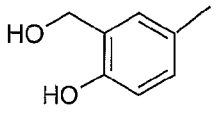
$-NH-SO_2R^{20}-$ where R^{20} is an alkyloxy group;

$-NH-R^{21}-$ where R^{21} is an alkyl or alkenyl group; optionally substituted by $COOR^{22}$ where R^{22} is C_{1-4} alkyl; or

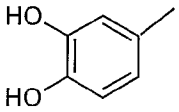
-NH-CO-S-;

wherein said alkyl, alkenyl and alkyloxy groups and moieties contain 1 or 2 carbon atoms.

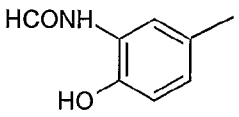
Particularly preferred groups (a) and (b) may be selected from the following groups (i) to (xxi):



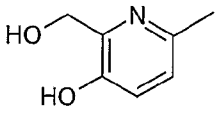
(i)



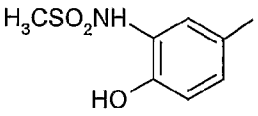
(ii)



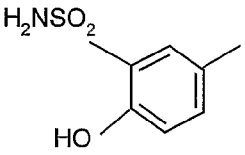
(iii)



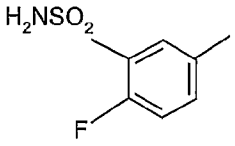
(iv)



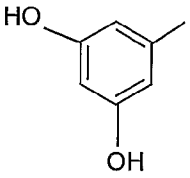
(v)



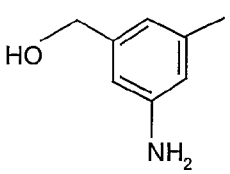
(vi)



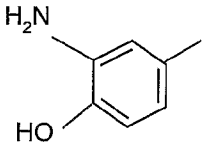
(vii)



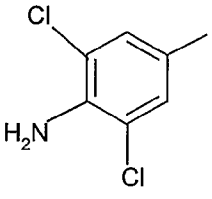
(viii)



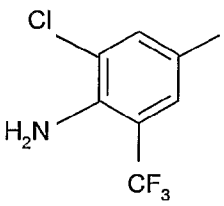
(ix)



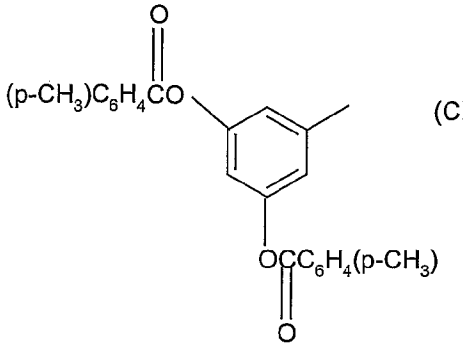
(x)



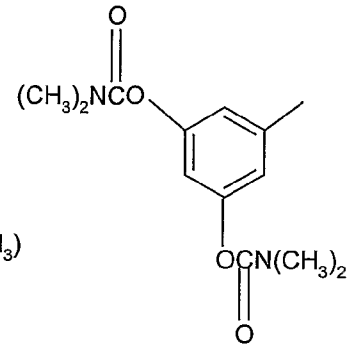
(xi)



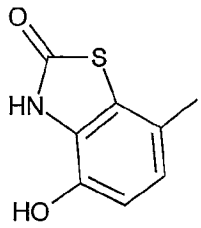
(xii)



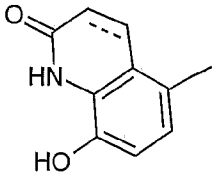
(xiii)



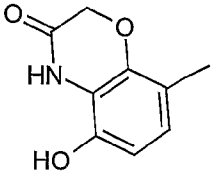
(xiv)



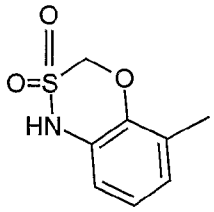
(xv)



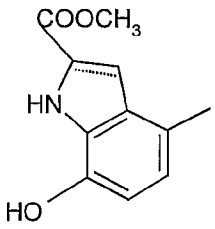
(xvi)



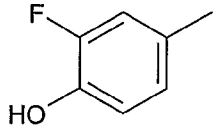
(xvii)



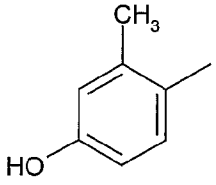
(xviii)



(xix)



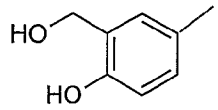
(xx)



(xxi)

wherein the dotted line in (xvi) and (xix) represents an optional double bond.

Most preferably Ar^1 is a group (i):



(i)

It is to be understood that the present invention covers all combinations of particular and preferred groups described hereinabove.

Preferred compounds of the invention include:

(2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]prop-2-enoic acid;

3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]propanoic acid;

(2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]prop-2-enoic acid;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-carboxylic acid;

[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]acetic acid;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxylic acid;

[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-yl]acetic acid;

[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]acetic acid;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-carboxylic acid;

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-N-isopropyl[1,1'-biphenyl]-2-sulfonamide;

N-Cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide;

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(morpholin-4-ylsulfonyl)[1,1'-biphenyl]-4-yl]butoxy}hexyl)amino]ethyl}phenol;

N-Ethyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-*N*-methyl[1,1'-biphenyl]-2-sulfonamide;

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide;

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide;

N-Cyclopropyl-3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide;

3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-sulfonamide;

N-[3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]urea;

N-cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxamide;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-ol;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-ol;

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-ol;

2-(hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(1*H*-tetraazol-5-yl)-1,1'-biphenyl-4-yl]butoxy}hexyl)amino]ethyl}phenol;

2-Hydroxy-5-[(1*R*)-1-hydroxy-2-({6-[4-(3'-hydroxy-1,1'-biphenyl-3-yl)butoxy]hexyl}amino)ethyl]phenylformamide with (2*E*)-but-2-enedioic acid (1:1);

and salts, solvates and physiologically functional derivatives thereof.

The compounds of formula (I) include an asymmetric centre, namely the carbon atom of the

group. The present invention includes both (S) and (R) enantiomers either in substantially pure form or admixed in any proportions. Preferably, the compounds of the invention are in the form of the (R) enantiomers.

Similarly, where R^4 and R^5 are different groups, the carbon atom to which they are attached is an asymmetric centre and the present invention includes both (S) and (R) enantiomers at this centre either in substantially pure form or admixed in any proportions.

Thus the compounds of formula (I) include all enantiomers and diastereoisomers as well as mixtures thereof in any proportions.

Salts and solvates of compounds of formula (I) which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives.

By the term "physiologically functional derivative" is meant a chemical derivative of a compound of formula (I) having the same physiological function as the free compound of formula (I) for example, by being convertible in the body thereto. According to the present invention, examples of physiologically functional derivatives include esters.

Suitable salts according to the invention include those formed with both organic and inorganic acids or bases. Pharmaceutically acceptable acid addition salts include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactic, pyruvic, acetic, trifluoroacetic, triphenylacetic, sulphamic, sulphanilic, succinic, oxalic, fumaric, maleic, malic, glutamic, aspartic, oxaloacetic, methanesulphonic, ethanesulphonic, arylsulphonic (for example p-toluenesulphonic, benzenesulphonic, naphthalenesulphonic or naphthalenedisulphonic), salicylic, glutaric, gluconic,

tricarballylic, cinnamic, substituted cinnamic (for example, phenyl, methyl , methoxy or halo substituted cinnamic, including 4-methyl and 4-methoxycinnamic acid), ascorbic, oleic, naphthoic, hydroxynaphthoic (for example 1- or 3-hydroxy-2-naphthoic), naphthaleneacrylic (for example naphthalene-2-acrylic), benzoic, 4-methoxybenzoic, 2- or 4-hydroxybenzoic, 4-chlorobenzoic, 4-phenylbenzoic, benzeneacrylic (for example 1,4-benzenediacrylic) and isethionic acids. Pharmaceutically acceptable base salts include ammonium salts, alkali metal salts such as those of sodium and potassium, alkaline earth metal salts such as those of calcium and magnesium and salts with organic bases such as dicyclohexyl amine and N-methyl-D-glucamine.

Pharmaceutically acceptable esters of the compounds of formula (I) may have a hydroxyl group converted to a C_{1-6}alkyl, aryl, aryl C_{1-6} alkyl, or amino acid ester.

As mentioned above, the compounds of formula (I) are selective β_2-adrenoreceptor agonists as demonstrated using functional or reporter gene readout from cell lines transfected with human beta-adrenoreceptors as described below. Compounds according to the present invention also have the potential to combine long duration of effect with rapid onset of action. Furthermore, certain compounds have shown an improved therapeutic index in animal models relative to existing long-acting β_2-agonist bronchodilators. As such, compounds of the invention may be suitable for once-daily administration.

Therefore, compounds of formula (I) and their pharmaceutically acceptable salts, solvates, and physiologically functional derivatives have use in the prophylaxis and treatment of clinical conditions for which a selective β_2-adrenoreceptor agonist is indicated. Such conditions include diseases associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary diseases (COPD) (e.g. chronic and wheezy bronchitis, emphysema), respiratory tract infection and upper respiratory tract disease.

Other conditions which may be treated include premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

Accordingly, the present invention provides a method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof. In particular, the present invention provides such a method for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect the present invention provides such a method for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

In the alternative, there is also provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy, particularly, for use in the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated. In particular, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) or muscle wasting disease.

The present invention also provides the use of a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated, for example a disease associated with reversible airways obstruction such as asthma, chronic obstructive pulmonary disease (COPD), respiratory tract infection or upper respiratory tract disease. In a further aspect, there is provided a compound of formula (I) or a pharmaceutically

acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition selected from premature labour, depression, congestive heart failure, skin diseases (e.g. inflammatory, allergic, psoriatic, and proliferative skin diseases), conditions where lowering peptic acidity is desirable (e.g. peptic and gastric ulceration) and muscle wasting disease.

The amount of a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof which is required to achieve a therapeutic effect will, of course, vary with the particular compound, the route of administration, the subject under treatment, and the particular disorder or disease being treated. The compounds of the invention may be administered by inhalation at a dose of from 0.0005mg to 10mg, preferably 0.005mg to 0.5mg, eg. 0.05mg to 0.5mg. The dose range for adult humans is generally from 0.0005 mg to 10mg per day and preferably 0.01mg to 1mg per day most preferably 0.05mg to 0.5mg per day.

While it is possible for a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof to be administered alone, it is preferable to present it as a pharmaceutical formulation.

Accordingly, the present invention further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

Hereinafter, the term "active ingredient" means a compound of formula (I) or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), inhalation (including fine particle dusts or mists which may be generated by means of various types of metered dose pressurised aerosols, nebulisers or insufflators), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing the active ingredient into association with the carrier which constitutes one or more accessory

ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example saline or water-for-injection, immediately prior to use. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Dry powder compositions for topical delivery to the lung by inhalation may, for example, be presented in capsules and cartridges of for example gelatine, or blisters of for example laminated aluminium foil, for use in an inhaler or insufflator. Powder blend formulations generally contain a powder mix for inhalation of the compound of the invention and a

suitable powder base (carrier/diluent/excipient substance) such as mono-, di or poly-saccharides (eg. lactose or starch). Use of lactose is preferred.

Each capsule or cartridge may generally contain between 20μg-10mg of the compound of formula (I) optionally in combination with another therapeutically active ingredient. Alternatively, the compound of the invention may be presented without excipients. Packaging of the formulation may be suitable for unit dose or multi-dose delivery. In the case of multi-dose delivery, the formulation can be pre-metered (eg as in Diskus, see GB 2242134, US Patent Nos. 6,632,666, 5,860,419, 5,873,360 and 5,590,645 or Diskhaler, see GB 2178965, 2129691 and 2169265, US Patent No.s 4,778,054, 4,811,731, 5,035,237, the disclosures of which are hereby incorporated by reference) or metered in use (eg as in Turbuhaler, see EP 69715 or in the devices described in US Patents No. 6,321,747 the disclosures of which are hereby incorporated by reference). An example of a unit-dose device is Rotahaler (see GB 2064336 and US Patent No. 4,353,656, the disclosures of which are hereby incorporated by reference). The Diskus inhalation device comprises an elongate strip formed from a base sheet having a plurality of recesses spaced along its length and a lid sheet hermetically but peelably sealed thereto to define a plurality of containers, each container having therein an inhalable formulation containing a compound of formula (I) preferably combined with lactose. Preferably, the strip is sufficiently flexible to be wound into a roll. The lid sheet and base sheet will preferably have leading end portions which are not sealed to one another and at least one of the said leading end portions is constructed to be attached to a winding means. Also, preferably the hermetic seal between the base and lid sheets extends over their whole width. The lid sheet may preferably be peeled from the base sheet in a longitudinal direction from a first end of the said base sheet.

Spray compositions for topical delivery to the lung by inhalation may for example be formulated as aqueous solutions or suspensions or as aerosols delivered from pressurised packs, such as a metered dose inhaler, with the use of a suitable liquefied propellant. Aerosol compositions suitable for inhalation can be either a suspension or a solution and generally contain the compound of formula (I) optionally in combination with another therapeutically active ingredient and a suitable propellant such as a fluorocarbon or hydrogen-containing chlorofluorocarbon or mixtures thereof, particularly hydrofluoroalkanes, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, especially 1,1,1,2-tetrafluoroethane, 1,1,1,2,3,3,3-heptafluoro-n-propane or a mixture thereof. Carbon dioxide or other suitable gas may also be used as propellant.

The aerosol composition may be excipient free or may optionally contain additional formulation excipients well known in the art such as surfactants eg oleic acid or lecithin and cosolvents eg ethanol. Pressurised formulations will generally be retained in a canister (eg an aluminium canister) closed with a valve (eg a metering valve) and fitted into an actuator provided with a mouthpiece.

Medicaments for administration by inhalation desirably have a controlled particle size. The optimum particle size for inhalation into the bronchial system is usually 1-10μm, preferably 2-5μm. Particles having a size above 20μm are generally too large when inhaled to reach the small airways. To achieve these particle sizes the particles of the active ingredient as produced may be size reduced by conventional means eg by micronisation. The desired fraction may be separated out by air classification or sieving. Preferably, the particles will be crystalline. When an excipient such as lactose is employed, generally, the particle size of the excipient will be much greater than the inhaled medicament within the present invention. When the excipient is lactose it will typically be present as milled lactose, wherein not more than 85% of lactose particles will have a MMD of 60-90μm and not less than 15% will have a MMD of less than 15μm.

Intranasal sprays may be formulated with aqueous or non-aqueous vehicles with the addition of agents such as thickening agents, buffer salts or acid or alkali to adjust the pH, isotonicity adjusting agents or anti-oxidants.

Solutions for inhalation by nebulation may be formulated with an aqueous vehicle with the addition of agents such as acid or alkali, buffer salts, isotonicity adjusting agents or antimicrobials. They may be sterilised by filtration or heating in an autoclave, or presented as a non-sterile product.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as gelatin and glycerin or sucrose an acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbefore recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The compounds and pharmaceutical formulations according to the invention may be used in combination with or include one or more other therapeutic agents, for example selected from anti-inflammatory agents, anticholinergic agents (particularly an M_1, M_2, M_1/M_2 or M_3 receptor antagonist), other β_2-adrenoreceptor agonists, antiinfective agents (e.g. antibiotics, antivirals), or antihistamines. The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with one or more other therapeutically active agents, for example selected from an anti-inflammatory agent (for example a corticosteroid or an NSAID), an anticholinergic agent, another β_2-adrenoreceptor agonist, an antiinfective agent (e.g. an antibiotic or an antiviral), or an antihistamine. Preferred are combinations comprising a compound of formula (I) or a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid, and/or an anticholinergic, and/or a PDE-4 inhibitor. Preferred combinations are those comprising one or two other therapeutic agents.

It will be clear to a person skilled in the art that, where appropriate, the other therapeutic ingredient(s) may be used in the form of salts, (e.g. as alkali metal or amine salts or as acid addition salts), or prodrugs, or as esters (e.g. lower alkyl esters), or as solvates (e.g. hydrates) to optimise the activity and/or stability and/or physical characteristics (e.g. solubility) of the therapeutic ingredient. It will be clear also that where appropriate, the therapeutic ingredients may be used in optically pure form.

Suitable anti-inflammatory agents include corticosteroids and NSAIDs. Suitable corticosteroids which may be used in combination with the compounds of the invention are those oral and inhaled corticosteroids and their pro-drugs which have anti-inflammatory activity. Examples include methyl prednisolone, prednisolone, dexamethasone, fluticasone propionate, 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-

hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, 6α,9α-difluoro-11β-hydroxy-16α-methyl-3-oxo-17α-propionyloxy- androsta-1,4-diene-17β-carbothioic acid *S*-(2-oxo-tetrahydro-furan-3S-yl) ester, beclomethasone esters (e.g. the 17-propionate ester or the 17,21-dipropionate ester), budesonide, flunisolide, mometasone esters (e.g. the furoate ester), triamcinolone acetonide, rofleponide, ciclesonide, butixocort propionate, RPR-106541, and ST-126. Preferred corticosteroids include fluticasone propionate, 6α,9α-difluoro-11β-hydroxy-16α-methyl-17α-[(4-methyl-1,3-thiazole-5-carbonyl)oxy]-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester and 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester, more preferably 6α,9α-difluoro-17α-[(2-furanylcarbonyl)oxy]-11β-hydroxy-16α-methyl-3-oxo-androsta-1,4-diene-17β-carbothioic acid *S*-fluoromethyl ester.

Suitable NSAIDs include sodium cromoglycate, nedocromil sodium, phosphodiesterase (PDE) inhibitors (e.g. theophylline, PDE4 inhibitors or mixed PDE3/PDE4 inhibitors), leukotriene antagonists, inhibitors of leukotriene synthesis, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine receptor agonists or antagonists (e.g. adenosine 2a agonists), cytokine antagonists (e.g. chemokine antagonists) or inhibitors of cytokine synthesis. Suitable other β_2-adrenoreceptor agonists include salmeterol (e.g. as the xinafoate), salbutamol (e.g. as the sulphate or the free base), formoterol (e.g. as the fumarate), fenoterol or terbutaline and salts thereof.

Of particular interest is use of the compound of formula (I) in combination with a phosphodiesterase 4 (PDE4) inhibitor or a mixed PDE3/PDE4 inhibitor. The PDE4-specific inhibitor useful in this aspect of the invention may be any compound that is known to inhibit the PDE4 enzyme or which is discovered to act as a PDE4 inhibitor, and which are only PDE4 inhibitors, not compounds which inhibit other members of the PDE family as well as PDE4. Generally it is preferred to use a PDE4 inhibitor which has an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity. For the purposes of this disclosure, the cAMP catalytic site which binds R and S rolipram with a low affinity is denominated the "low affinity" binding site (LPDE 4) and the other form of this catalytic site which binds rolipram with a high affinity is denominated the "high affinity" binding site (HPDE 4). This term "HPDE4" should not be confused with the term "hPDE4" which is used to denote human PDE4.

A method for determining IC_{50}s ratios is set out in US patent 5,998,428 which is incorporated herein in full by reference as though set out herein. See also PCT application WO 00/51599 for an another description of said assay.

The preferred PDE4 inhibitors of use in this invention will be those compounds which have a salutary therapeutic ratio, i.e., compounds which preferentially inhibit cAMP catalytic activity where the enzyme is in the form that binds rolipram with a low affinity, thereby reducing the side effects which apparently are linked to inhibiting the form which binds rolipram with a high affinity. Another way to state this is that the preferred compounds will have an IC_{50} ratio of about 0.1 or greater as regards the IC_{50} for the PDE4 catalytic form which binds rolipram with a high affinity divided by the IC_{50} for the form which binds rolipram with a low affinity.

A further refinement of this standard is that of one wherein the PDE4 inhibitor has an IC_{50} ratio of about 0.1 or greater; said ratio is the ratio of the IC_{50} value for competing with the binding of 1nM of [^{3}H]R-rolipram to a form of PDE4 which binds rolipram with a high affinity over the IC_{50} value for inhibiting the PDE4 catalytic activity of a form which binds rolipram with a low affinity using 1 μM[^{3}H]-cAMP as the substrate.

Most preferred are those PDE4 inhibitors which have an IC_{50} ratio of greater than 0.5, and particularly those compounds having a ratio of greater than 1.0. Preferred compounds are *cis* 4-cyano-4-(3-cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-carboxylic acid, 2-carbomethoxy-4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-one and *cis*-[4-cyano-4-(3-cyclopropylmethoxy-4-difluoromethoxyphenyl)cyclohexan-1-ol]; these are examples of compounds which bind preferentially to the low affinity binding site and which have an IC_{50} ratio of 0.1 or greater.

Other compounds of interest include:

Compounds set out in U.S. patent 5,552,438 issued 03 September, 1996; this patent and the compounds it discloses are incorporated herein in full by reference. The compound of particular interest, which is disclosed in U.S. patent 5,552,438, is *cis*-4-cyano-4-[3-(cyclopentyloxy)-4-methoxyphenyl]cyclohexane-1-carboxylic acid (also known as cilomalast) and its salts, esters, pro-drugs or physical forms;

AWD-12-281 from elbion (Hofgen, N. et al. 15th EFMC Int Symp Med Chem (Sept 6-10, Edinburgh) 1998, Abst P.98; CAS reference No. 247584020-9); a 9-benzyladenine derivative nominated NCS-613 (INSERM); D-4418 from Chiroscience and Schering-Plough; a benzodiazepine PDE4 inhibitor identified as CI-1018 (PD-168787) and attributed to Pfizer; a benzodioxole derivative disclosed by Kyowa Hakko in WO99/16766; K-34 from Kyowa Hakko; V-11294A from Napp (Landells, L.J. et al. Eur Resp J [Annu Cong Eur Resp Soc (Sept 19-23, Geneva) 1998] 1998, 12 (Suppl. 28): Abst P2393); roflumilast (CAS reference No 162401-32-3) and a pthalazinone (WO99/47505, the disclosure of which is hereby incorporated by reference) from Byk-Gulden; Pumafentrine, (-)-p-[(4*a*R*,10*b*S*)-9-ethoxy-1,2,3,4,4a,10b-hexahydro-8-methoxy-2-methylbenzo[c][1,6]naphthyridin-6-yl]-N,N-diisopropylbenzamide which is a mixed PDE3/PDE4 inhibitor which has been prepared and published on by Byk-Gulden, now Altana; arofylline under development by Almirall-Prodesfarma; VM554/UM565 from Vernalis; or T-440 (Tanabe Seiyaku; Fuji, K. et al. J Pharmacol Exp Ther,1998, 284(1): 162), and T2585.

Other possible PDE-4 and mixed PDE3/PDE4 inhibitors include those listed in WO01/13953, the disclosure of which is hereby incorporated by reference.

Suitable anticholinergic agents are those compounds that act as antagonists at the muscarinic receptor, in particular those compounds which are antagonists of the M_1 and M_2 receptors. Exemplary compounds include the alkaloids of the belladonna plants as illustrated by the likes of atropine, scopolamine, homatropine, hyoscyamine; these compounds are normally administered as a salt, being tertiary amines. These drugs, particularly the salt forms, are readily available from a number of commercial sources or can be made or prepared from literature data via, to wit:

Atropine - CAS-51-55-8 or CAS-51-48-1 (anhydrous form), atropine sulfate - CAS-5908-99-6; atropine oxide - CAS-4438-22-6 or its HCl salt - CAS-4574-60-1 and methylatropine nitrate - CAS-52-88-0.

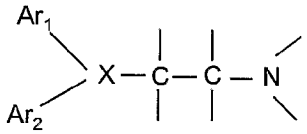
Homatropine - CAS-87-00-3, hydrobromide salt - CAS-51-56-9, methylbromide salt - CAS-80-49-9.

Hyoscyamine (*d*, *l*) - CAS-101-31-5, hydrobromide salt - CAS-306-03-6 and sulfate salt - CAS-6835-16-1.

Scopolamine - CAS-51-34-3, hydrobromide salt - CAS-6533-68-2, methylbromide salt-CAS-155-41-9.

Preferred anticholinergics include ipratropium (e.g. as the bromide), sold under the name Atrovent, oxitropium (e.g. as the bromide) and tiotropium (e.g. as the bromide) (CAS-139404-48-1). Also of interest are: methantheline (CAS-53-46-3), propantheline bromide (CAS- 50-34-9), anisotropine methyl bromide or Valpin 50 (CAS- 80-50-2), clidinium bromide (Quarzan, CAS-3485-62-9), copyrrolate (Robinul), isopropamide iodide (CAS-71-81-8), mepenzolate bromide (U.S. patent 2,918,408), tridihexethyl chloride (Pathilone, CAS-4310-35-4), and hexocyclium methylsulfate (Tral, CAS-115-63-9). See also cyclopentolate hydrochloride (CAS-5870-29-1), tropicamide (CAS-1508-75-4), trihexyphenidyl hydrochloride (CAS-144-11-6), pirenzepine (CAS-29868-97-1), telenzepine (CAS-80880-90-9), AF-DX 116, or methoctramine, and the compounds disclosed in WO01/04118, the disclosure of which is hereby incorporated by reference.

Suitable antihistamines (also referred to as H_1-receptor antagonists) include any one or more of the numerous antagonists known which inhibit H_1-receptors, and are safe for human use. All are reversible, competitive inhibitors of the interaction of histamine with H_1-receptors. The majority of these inhibitors, mostly first generation antagonists, have a core structure, which can be represented by the following formula:



This generalized structure represents three types of antihistamines generally available: ethanolamines, ethylenediamines, and alkylamines. In addition, other first generation antihistamines include those which can be characterized as based on piperizine and phenothiazines. Second generation antagonists, which are non-sedating, have a similar structure-activity relationship in that they retain the core ethylene group (the alkylamines) or mimic the tertiary amine group with piperizine or piperidine. Exemplary antagonists are as follows:

Ethanolamines: carbinoxamine maleate, clemastine fumarate, diphenylhydramine hydrochloride, and dimenhydrinate.

Ethylenediamines: pyrilamine amleate, tripelennamine HCl, and tripelennamine citrate.

Alkylamines: chloropheniramine and its salts such as the maleate salt, and acrivastine.

Piperazines: hydroxyzine HCl, hydroxyzine pamoate, cyclizine HCl, cyclizine lactate, meclizine HCl, and cetirizine HCl.

Piperidines: Astemizole, levocabastine HCl, loratadine or its descarboethoxy analogue, and terfenadine and fexofenadine hydrochloride or another pharmaceutically acceptable salt.

Azelastine hydrochloride is yet another H_1 receptor antagonist which may be used in combination with a PDE4 inhibitor.

Examples of preferred anti-histamines include methapyrilene and loratadine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an antihistamine.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with a PDE4 inhibitor and a corticosteroid.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) a pharmaceutically acceptable salt, solvate or physiologically functional derivative thereof together with an anticholinergic and a PDE-4 inhibitor.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a physiologically acceptable diluent or carrier represent a further aspect of the invention.

The individual compounds of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations. Appropriate doses of known therapeutic agents will be readily appreciated by those skilled in the art.

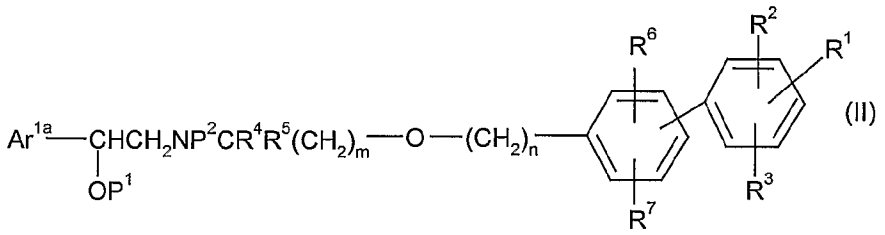
According to a further aspect of the invention, there is provided a process for preparing a compound of formula (I) or a salt, solvate, or physiologically functional derivative thereof which comprises a process as defined below, followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

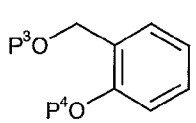
In one general process (a), a compound of formula (I), may be obtained by deprotection of a protected intermediate, for example of formula (II):



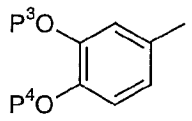
(II)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m, and n are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1; and P^1 and P^2 are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group.

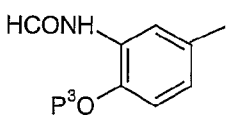
Protected forms of the preferred groups Ar^1 may be selected from:



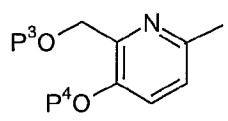
(ia)



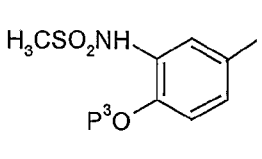
(iia)



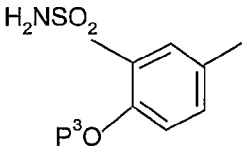
(iiia)



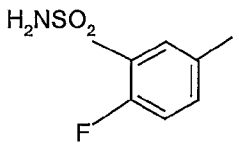
(iva)



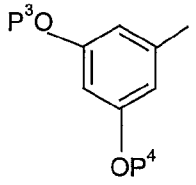
(va)



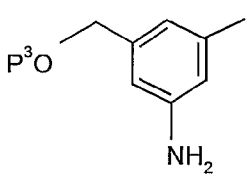
(via)



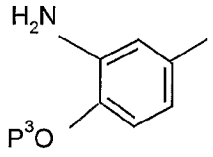
(viia)



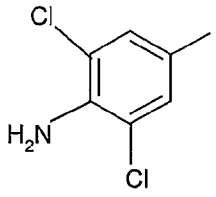
(viiia)



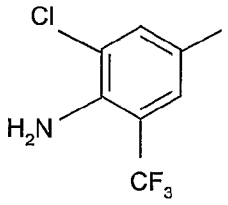
(ixa)



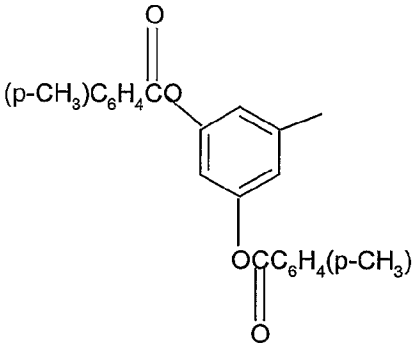
(xa)



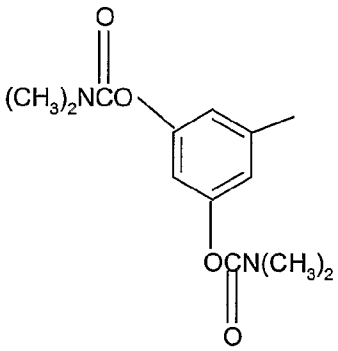
(xia)



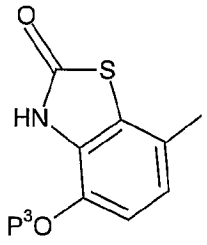
(xiia)



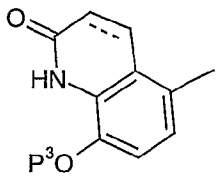
(xiiia)



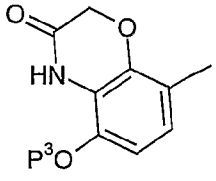
(xiva)



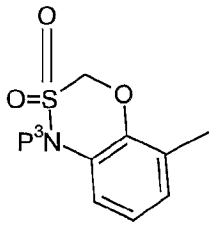
(xva)



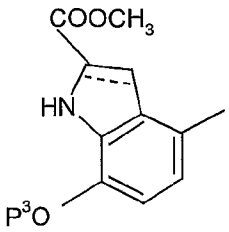
(xvia)



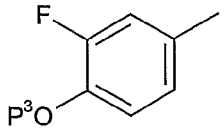
(xviia)



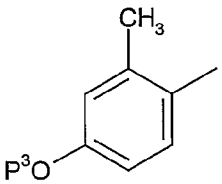
(xviiia)



(xixa)



(xxa)



(xxia)

wherein P^3 and P^4 are each independently either hydrogen or a protecting group provided that at least one of P^3 and P^4 is a protecting group, and the dotted line in (xvia) and (xixa) denotes an optional double bond. It will be appreciated from the foregoing structures that where Ar^1 is a group (vii), (xi), (xii), (xiii) or (xiv) protection is not required.

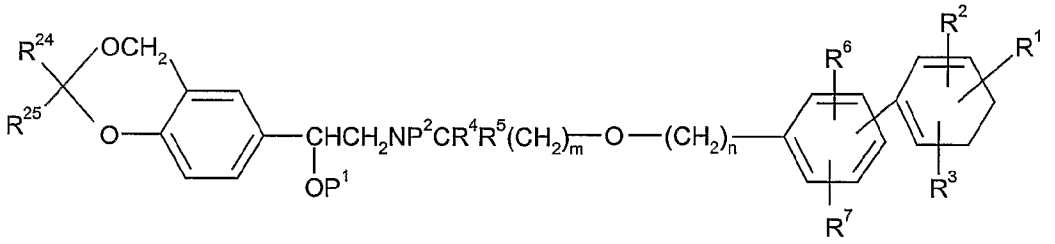
Suitable protecting groups may be any conventional protecting group such as those described in "Protective Groups in Organic Synthesis" by Theodora W Greene and Peter G M Wuts, 3rd edition (John Wiley & Sons, 1999). Examples of suitable hydroxyl protecting groups represented by P^3 and P^4 are esters such as acetate ester, aralkyl groups such as benzyl, diphenylmethyl, or triphenylmethyl, and tetrahydropyranyl. Examples of suitable amino protecting groups represented by P^2 include benzyl, α-methylbenzyl, diphenylmethyl, triphenylmethyl, benzyloxycarbonyl, tert-butoxycarbonyl, and acyl groups such as trichloroacetyl or trifluoroacetyl.

As will be appreciated by the person skilled in the art, use of such protecting groups may include orthogonal protection of groups in the compounds of formula (II) to facilitate the selective removal of one group in the presence of another, thus enabling selective functionalisation of a single amino or hydroxyl function. For example, the –CH(OH) group may be orthogonally protected as – $CH(OP^1)$ using, for example, a trialkylsilyl group such as triethylsilyl. A person skilled in the art will also appreciate other orthogonal protection strategies, available by conventional means as described in Theodora W Greene and Peter G M Wuts (see above).

The deprotection to yield a compound of formula (I), may be effected using conventional techniques. Thus, for example, when P^2, P^3, and/or P^4 is an aralkyl group, this may be

cleaved by hydrogenolysis in the presence of a metal catalyst (e.g. palladium on charcoal).

When P^3 and/or P^4 is tetrahydropyranyl this may be cleaved by hydrolysis under acidic conditions. Acyl groups represented by P^2 may be removed by hydrolysis, for example with a base such as sodium hydroxide, or a group such as trichloroethoxycarbonyl may be removed by reduction with, for example, zinc and acetic acid. Other deprotection methods may be found in Theodora W Greene and Peter G M Wuts (see above). In a particular embodiment of process (a), P^3 and P^4 may together represent a protecting group as in the compound of formula (III):



(III)

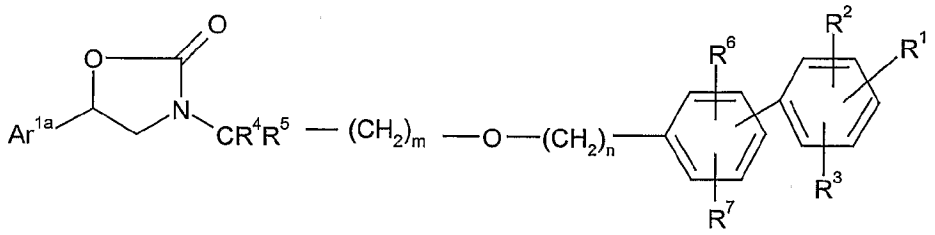
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, P^1, P^2, m, and n are as defined for the compound of formula (I), R^{24} and R^{25} are independently selected from hydrogen, C_{1-6}alkyl, or aryl or R^{24} and R^{25} together form a C_{3-7}cycloalkyl ring. In a preferred aspect, both R^{24} and R^{25} are methyl.

The compound of formula (III) may be converted to a compound of formula (I), by hydrolysis with dilute aqueous acid, for example acetic acid or hydrochloric acid in a suitable solvent or by transketalisation in an alcohol, for example ethanol, in the presence of a catalyst such as an acid (for example, toluenesulphonic acid) or a salt (such as pyridinium tosylate) at normal or elevated temperature.

It will be appreciated that the protecting groups P^1, P^2, P^3 and P^4 (including the cyclised protecting group formed by P^3 and P^4 as depicted in formula (III) may be removed in a single step or sequentially. The precise order in which protecting groups are removed will in part depend upon the nature of said groups and will be readily apparent to the skilled worker. Preferably, when P^3 and P^4 together form a protecting group as in formula (III)

this protecting group is removed together with any protecting group on the CH(OH) moiety, followed by removal of P^2.

Compounds of formulae (II) and (III) wherein P^1 and P^2 represent hydrogen may be prepared from the corresponding compound of formula (IV):

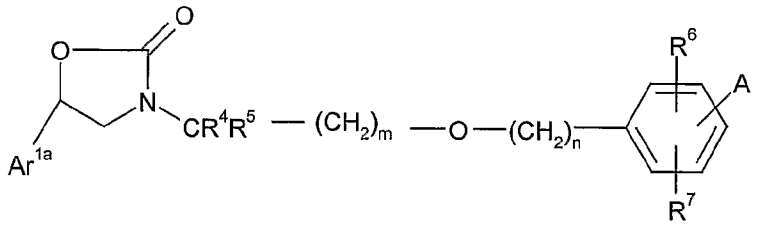


(IV)

or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, Ar^{1a}, m, and n are as defined for the compound of formula (II) or (III).

The conversion of a compound of formula (IV) to a compound of formula (II) or (III) may be effected by treatment with a base, for example a non-aqueous base, such as potassium trimethylsilanolate, or an aqueous base such as aqueous sodium hydroxide, in a suitable solvent such as tetrahydrofuran.

Compounds of formula (IV) may be prepared from the corresponding compound of formula (V):



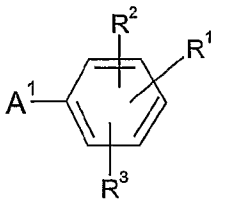
(V)

or a salt or solvate thereof, wherein R^4, R^5, R^6, R^7, Ar^{1a}, m and n are as defined for the compound of formula (II) and A is either

(i) a leaving group group such as halo, eg. bromo or iodo, preferably iodo; or a haloalkylsulphonate such as trifluoromethane sulfonate; or

(ii) a reactive group selected from boronic acid, or a boronic acid ester or an organo-zinc or organo-tin moiety;

by coupling with a compound of formula (VI):


(VI)

wherein R^1, R^2 and R^3 are as defined for formula (I)

and A^1 is either:

(i) a leaving group group such as halo, eg. bromo or iodo, preferably iodo; or a haloalkylsulphonate such as trifluoromethane sulfonate; or

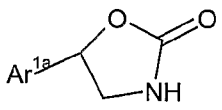
(ii) a reactive group selected from boronic acid, or a boronic acid ester or an organo-zinc or organo-tin moiety;

provided that when A is selected from a leaving group (i) then A^1 is selected from a reactive group (ii) and *vice versa.*

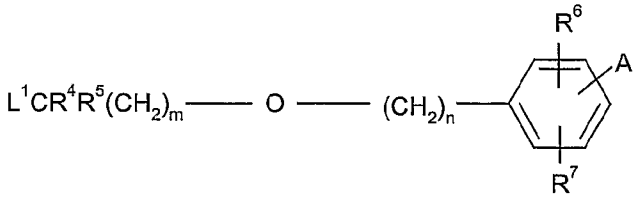
When either A or A^1 represents a boronic acid ester, this should be an ester which is hydrolysed *in situ* to the boronic acid.

The coupling of a compound of formula (V) with a compound of formula (VI) is conveniently effected in the presence of a catalyst system such as palladium, for example, tetrakis(triphenylphosphine) palladium (0) or bis(diphenylphosphino)ferrocene palladium dichloride with a base such as sodium carbonate or caesium carbonate, in a suitable solvent for example 1,2- dimethoxyethane, or N,N-dimethylformamide.

Compounds of formula (V) may be prepared by coupling a compound of formula (VII):


(VII)

or a salt or solvate thereof, wherein Ar^{1a} is defined for the compound of formula (V) with a compound of formula (VIII):



(VIII)

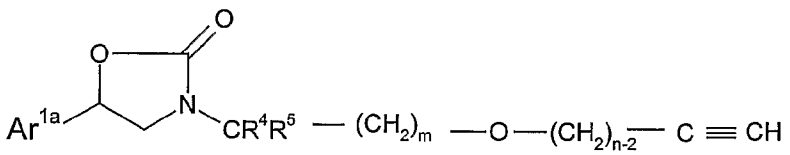
wherein, R^4, R^5, R^6, R^7, A, m and n are as defined for the compound of formula (V) and L^1 is a leaving group for example a halo group, (typically bromo or iodo) or a sulfonate such as an alkyl sulfonate (typically methanesulfonate) an aryl sulfonate (typically toluenesulfonate) or a haloalkylsulfonate (typically trifluoromethane sulfonate).

The coupling of a compound of formula (VII) with a compound of formula (VIII) may be effected in the presence of a base, such as a metal hydride, for example sodium hydride, or an inorganic base such as cesium carbonate, in an aprotic solvent, for example N,N-dimethylformamide or tetrahydrofuran.

When the group A in the compound of formula (V) represents a leaving group, this may if desired be converted into a boronic acid derivative, by reaction with bis(pinacolato)diboron and 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride in the presence of potassium acetate and in a solvent such as a mixture of dichloromethane and N,N-dimethylformamide.

Compounds of formula (VII) may be prepared as described for example in WO02/066422.

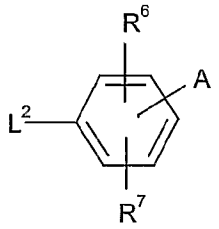
Alternatively, compounds of formula (V) may be prepared from a corresponding alkyne of formula (IX):



(IX)

wherein Ar^{1a}, R^4, R^5, m and n are as defined for formula (II);

by coupling with a compound of formula (X):



(X)

wherein R^6, R^7 and A are as defined hereinabove for compounds of formula (V) and L^2 is a leaving group for example a halo group, (typically bromo or iodo) or a haloalkylsulfonate (typically trifluoromethane sulfonate), followed by reduction.

The coupling of a compound of formula (IX) with a compound of formula (X) or a precursor thereof is conveniently effected in the presence of a catalyst system such as bis(triphenylphosphino) palladium dichloride and a copper catalyst such as cuprous iodide, with an organic base such as a trialkylamine, for example triethylamine, in a suitable solvent for example acetonitrile or dimethylformamide. The resulting alkyne may then be reduced, either with or without being isolated to form the compound of formula (V). The reduction may be effected by any suitable method such as hydrogenation in the presence of a catalyst, for example palladium/charcoal or platinum oxide.

Compounds of formula (IX) may be prepared for example as described in WO 02/070490.

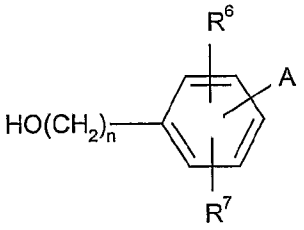
Compounds of formula (X) may be prepared by standard methods well known to those skilled in the art.

A compound of formula (VIII) may be prepared from a corresponding compound of formula (XI):

$$L^1CR^4R^5(CH_2)_mL^1 \qquad (XI)$$

wherein R^4, R^5 and m are as defined for compounds of formula (I) and each L^1, which may be the same or different, represents a leaving group eg. as defined above for compounds of formula (VIII);

by reaction with an alcohol of formula (XII):



(XII)

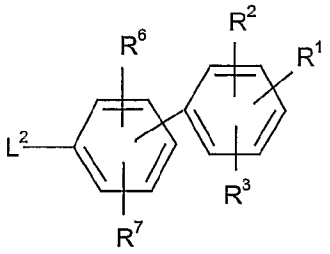
wherein R^6, R^7, A and n are as defined for compounds of formula (VIII).

The coupling of compounds (XI) and (XII) may be effected in the presence of an inorganic base, such as aqueous sodium hydroxide, under phase transfer conditions in the presence of an ammonium salt such as a tetraalkylammonium bromide, e.g.tetrabutylammonium bromide.

It will be appreciated that when the group A in compounds of formula (VIII) initially obtained represents bromo, this may, if desired, be exchanged for an iodo substituent by reaction with iodine in the presence of an alkyl lithium, such as n-butyl lithium, in a solvent such as tetrahydrofuran.

Compounds of formula (XII) are known in the art, for example EP 995752A, or may be prepared by standard methods.

A compound of formula (IV) may also be preapred by reacting a compound of formula (XIII):



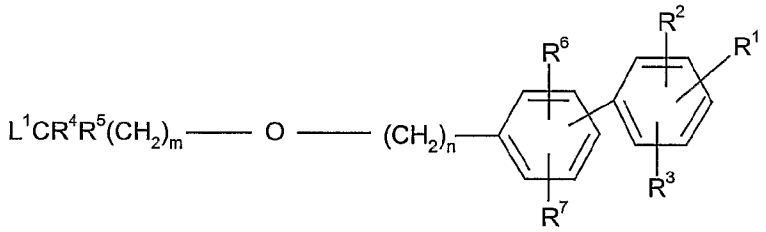
(XIII)

wherein L^2 is a leaving group as defined for compounds of formula (X) above;

with a compound of formula (IX) as hereinbefore defined, in an analogous manner to the coupling of a compound of formula (IX) with a compound of formula (X) as described hereinabove.

A compound of formula (XIII) may be prepared by coupling a compound of formula (X) as defined hereinabove with a compound of formula (VI) as defined hereinabove, in an analogous manner to the coupling of a compound of formula (V) with a compound of formula (VI), as described hereinabove.

A compound of formula (IV) may also be prepared by coupling a compound of formula (VII) with a compound of formula (XIV):

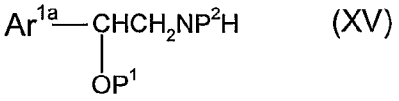


(XIV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m and n are as defined for formula (II) and L^1 is as defined for formula (VIII);

in an analogous manner to process (b) below.

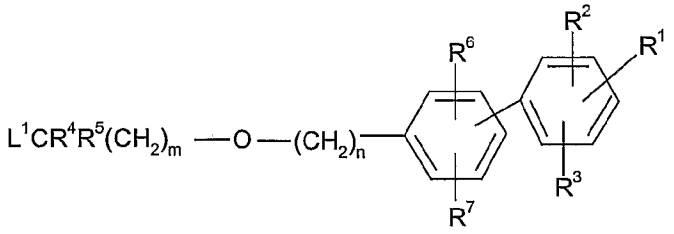
Thus in a further process (b) a compound of formula (I) may be obtained by alkylation of an amine of formula (XV):



(XV)

wherein Ar^{1a}, P^1 and P^2 are as defined for formula (II);

with a compound of formula (XIV):



(XIV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 m and n are as defined for formula (II) and L^1 is as defined for formula (VIII);

followed by removal of any protecting groups present by conventional methods as described above for the deprotection of compounds of formula (II).

The reaction of compounds of formulae (XIII) and (XIV) is optionally effected in the presence of an organic base such as a trialkylamine, for example, diisopropylethylamine, and in a suitable solvent for example N,N-dimethylformamide.

Compounds of formula (XV) are known in the art (for example EP-A 0947498 or WO 02/070490) or may be readily prepared by a person skilled in the art.

Further details concerning preparation of compounds (XV) wherein Ar^1 is a group (v) can be found in DE3524990; concerning the preparation of compounds (XV) wherein Ar^1 is a group (ii), (viii), and (xvi) in EP-A-162576; concerning the preparation of compounds (XV) wherein Ar^1 is a group (iv) in EP-A-220054; concerning the preparation of compounds (XV) wherein Ar^1 is a group (xi) in GB2165542 and concerning the preparation of compounds (XV) wherein Ar^1 is a group (c) in GB2230523.

A compound of formula (XIV) may be prepared from a compound of formula (VIII) by reaction with a compound (VI) in an analogous manner to the reaction of a compound of formula (V) with a compound of formula (VI).

It will be appreciated that the precise order of the synthetic steps by which the various groups and moieties are introduced into the molecule may be varied. It will be within the skill of the practitioner in the art to ensure that groups or moieties introduced at one stage of the process will not be affected by subsequent transformations and reactions, and to select the order of synthetic steps accordingly.

The enantiomeric compounds of the invention may be obtained (i) by separation of the components of the corresponding racemic mixture, for example, by means of a chiral chromatography column, enzymic resolution methods, or preparing and separating suitable diastereoisomers, or (ii) by direct synthesis from the appropriate chiral intermediates by the methods described above.

Optional conversions of a compound of formula (I) to a corresponding salt may conveniently be effected by reaction with the appropriate acid or base. Optional conversion of a compound of formula (I) to a corresponding solvate or physiologically functional derivative may be effected by methods known to those skilled in the art.

According to a further aspect, the present invention provides novel intermediates for the preparation of compounds of formula (I) for example, compounds of formula (II), (III) and (IV) as defined above, or an optical isomer, a salt, or a protected derivative thereof.

For a better understanding of the invention, the following Examples are given by way of illustration.

SYNTHETIC EXAMPLES

Throughout the examples, the following abbreviations are used:

LCMS: Liquid Chromatography Mass Spectrometry

MS : mass spectrum

TSP+ve : thermospray mass spectrum positive mode

HPLC: high pressure liquid chromatography

RT : retention time

THF : tetrahydofuran

DCM : dichloromethane

DMF : N,N-dimethylformamide

EtOAc : ethyl acetate

Et_2O : diethyl ether

EtOH : ethanol

MeOH : methanol

bp : boiling point

ca : circa

h : hour(s)

min : minute(s)

All temperatures are given in degrees centigrade.

Silica gel refers to Merck silica gel 60 Art number 7734.

Flash silica gel refers to Merck silica gel 60 Art number 9385.

Biotage refers to prepacked silica gel cartridges containing KP-Sil run on flash 12i chromatography module.

Bond Elut are prepacked cartridges used in parallel purifications, normally under vacuum. These are commercially available from Varian.

LCMS was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 min 0%B, 0.7-4.2 min 100%B, 4.2-5.3 min 100%B, 5.3-5.5 min 0%B at a flow rate of 3 ml/min. The mass spectra were recorded on a Fisons VG Platform spectrometer using electrospray positive and negative mode (ES+ve and ES-ve).

HPLC was conducted on a LCABZ+PLUS column (3.3 cm x 4.6 mm ID) eluting with 0.1% formic acid and 0.01 M ammonium acetate in water (solvent A), and 0.05% formic acid 5% water in acetonitrile (solvent B) using the following elution gradient 0-1 min 0%B, 1-10 min100%B, 10-13 min 100%B, 13-15 min 0%B at a flow rate of 1ml/min

Example 1

(2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]prop-2-enoic acid acetate

i) 6-Bromohexyl 4-(3-bromophenyl)butyl ether

A stirred mixture of 4–(3-bromophenyl) butan-1-ol (18 g) (EP 0 995 752A1), 1,6 dibromohexane (48 ml), tetrabutylammonium bromide (1.5 g) and 50% aqueous sodium hydroxide solution (500 ml) was stirred for 2 days at ambient temperature. The mixture

was poured into water (1000 ml) and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified on a biotage cartridge (90 g) eluting with light petroleum (40-60 °C), and then light petroleum (40-60 °C) - ether (9:1). The appropriate fractions were evaporated to give *the title compound* (18 g). LCMS RT= 4.34 min.

ii) 6-Bromohexyl 4-(3-iodophenyl)butyl ether

A solution of n-butyl lithium in hexane (1.6 M; 50 ml) was added to a stirred solution of 6-bromohexyl 4-(3-bromophenyl)butyl ether (21 g) in dry THF (150 ml) at –85 °C under nitrogen. After 15 min a solution of iodine (19.8 g) in THF (100 ml) was added dropwise over 20 min. The solution was then allowed to warm up to 0 °C and aqueous sodium bisulphite was added. The mixture was poured into water and extracted into ether. The combined extracts were dried (Na_2SO_4) and evaporated. The residue was purified by flash silica gel column chromatography (1 kg) eluting with cyclohexane – ether (9:1). The appropriate fractions were evaporated to give *the title compound* (17 g). LCMS RT = 4.41 min.

iii) (5R)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one

Sodium hydride (60% oil dispersion, 1.26 g) was added to a stirred, cooled (ice-bath) solution of (5*R*)-5-(4*H*-1,3-benzodioxin-6-yl)-2-oxazolidinone (5.47 g) in dry DMF (50 ml) under nitrogen and the mixture was stirred for 15 min at 5 °C. A solution of 6-bromohexyl 4-(3-iodophenyl)butyl ether (10.7 g) in DMF (30 ml) was then added dropwise over 10 min. The mixture was stirred for 2 h at ambient temperature, then poured into aqueous solution of ammonium chloride and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residue was purified on a biotage cartridge (90 g) eluting with ether - hexane (3:2) to give *the title compound* (9.8 g). LCMS RT= 4.20 min.

iv) Methyl (2*E*)-3-{3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-yl}prop-2-enoate

To a solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one (220mg) in 1,2-dimethoxyethane (3 ml) and aqueous sodium carbonate solution (2M, 2 ml) were added (3-methoxy-3-oxo-1-propen-1-yl)phenyl boronic acid (94.9 mg), and tetrakis(triphenylphosphine) palladium (0)

(10 mg). The mixture was heated to 80 °C under nitrogen for 1h. Water was then added and the mixture was extracted into ethyl acetate, dried (Na_2SO_4) and concentrated in vacuo to give *the title compound* (150 mg). LCMS RT = 4.35 min.

v) (2*E*)-3-(3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4H-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-yl)prop-2-enoic acid

To a solution of methyl (2*E*)-3-{3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-yl}prop-2-enoate (143mg) in tetrahydrofuran (3 ml) was added potassium trimethylsilanolate (84 mg). The mixture was stirred and heated at 80 °C for 1h. Water was added to the reaction mixture and the product was extracted into ethyl acetate. The organic layer was dried (Na_2SO_4) and concentrated in vacuo to give *the title compound* (100 mg). LCMS RT = 3.26 min.

vi) (2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]prop-2-enoic acid acetate

A mixture of (2*E*)-3-(3'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-yl)prop-2-enoic acid (100 mg) in acetic acid (3 ml) and water (1ml) was heated to 80°C for 1h. The mixture was concentrated *in vacuo* to give *the title compound* (90 mg). LCMS RT= 3.09 min; ES+ve 562 (MH^+).

Example 2

3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]propanoic acid acetate

i) Methyl 3-{3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-4-yl}propanoate

Prepared using methods similar to those described in Example 1 iv) LCMS RT = 4.29 min.

ii) 3-(3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-4-yl)propanoic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.25 min.

iii) 3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]propanoic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 3.28 min, ES+ve 564 (MH^+).

Example 3

(2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]prop-2-enoic acid acetate

i) Methyl (2*E*)-3-{3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-4-yl}prop-2-enoate

Prepared using methods similar to those described in Example 1 iv) LCMS RT = 4.41 min

ii) (2*E*)-3-(3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-4-yl)prop-2-enoic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.25 min

iii) (2*E*)-3-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]prop-2-enoic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT 3.08 min, ES+ve 562 (MH^+).

Example 4

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-carboxylic acid acetate

i) Methyl 3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-carboxylate

Prepared using methods similar to those described in Example 1 iv) LCMS RT = 4.32 min

ii) 3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-carboxylic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.29 min

iii) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-carboxylic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.95 min, ES+ve 536 (MH^+).

Example 5

[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]acetic acid acetate

i) Methyl {3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-4-yl}acetate

Prepared using methods similar to those described in Example 1 iv) LCMS RT = 4.17 min

ii) (3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-4-yl)acetic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.24 min.

iii) [3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-yl]acetic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 3.00 min, ES+ve 550 (MH^+).

Example 6

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxylic acid acetate

i) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one

A stirred mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one (1.0 g), bis(pinacolato)diboron (0.628g), potassium acetate (485 mg) and 1,1' -bis(diphenylphosphino) ferrocene palladium dichloride complex with dichloromethane (60 mg) in dimethylformamide (25ml) was heated at 80° under nitrogen for 20 h. The mixture was cooled and poured into water and extracted into ethyl acetate. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (90 g) eluting with ether-petroleum ether (40-60°) to give *the title compound* (700 mg). LCMS RT = 4.35 min.

ii) Methyl 3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxylate

A mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one (100 mg), methyl 2-iodobenzoate (65 mg) and potassium carbonate (114 mg) in 1,2-dimethoxyethane (4 ml) was heated to 95°C under nitrogen. 1,1-Bis(diphenylphosphino)ferrocene palladium dichloride (50 mg) was added and the mixturewas heated for 4 h. The reaction mixture was poured into water and extracted into ethyl acetate. The organic layer was dried and evaporated to dryness. The residue was purified on a Bond Elut cartridge (10 g) eluting with DCM and then ether to give *the title compound* (90 mg). LCMS RT 4.14 min

iii) 3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-2-carboxylic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.09 min

iv) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxylic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.82 min, ES+ve 536 (MH^+).

Example 7

[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-yl]acetic acid acetate

i) Methyl {3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-yl}acetate
Prepared using methods similar to those described in Example 6 ii) LCMS RT = 4.15 min

ii) (3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-2-yl)acetic acid
Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.05 min

iii) [3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-yl]acetic acid acetate
Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.81 min, ES+ve 550 (MH^+).

Example 8
[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]acetic acid acetate

i) Methyl {3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-yl}acetate
Prepared using methods similar to those described in Example 6 ii) LCMS RT = 4.12 min

ii) (3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-yl)acetic acid
Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.05 min

iii) [3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]acetic acid acetate
Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.90 min, ES+ve 550 (MH^+).

Example 9
3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-carboxylic acid

acetate

i) (5*R*)-3-[6-(But-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (4 g) in DMF (25 ml) was added to a suspension of sodium hydride (60% oil dispersion, 1.32 g) in DMF (10 ml) at 0 °C and the mixture was stirred for 10 min. A solution of 6-bromohexyl but-3-ynyl ether (5 g) in DMF (15 ml) was added and the cooling bath was removed. The mixture was stirred for 18 h and then concentrated under reduced pressure. The residue was purified by column chromatography on flash silica gel eluting with heptane-ether (2:1) and then with neat ether to give *the title compound* (5.8 g). LCMS RT = 3.26 min.

ii) 2-(3-Iodophenyl)-4,6-diphenyl-1,3,2-dioxaborinane

A mixture of 3-iodophenylboronic acid (15 g) and 1,3-diphenyl-1,3-propanediol (15 g) in tetrahydrofuran (150 ml) was heated to reflux for 15 min in the presence of molecular sieves. The mixture was filtered and the filtrate was concentrated under reduced pressure. The residue was crystallised from heptane – ethyl acetate (5:1) to give *the title compound* (25.3 g) LCMS RT = 3.03 min.

iii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-({4-[3-(4,6-diphenyl-1,3,2-dioxaborinan-2-yl)phenyl]but-3-ynyl}oxy)hexyl]-1,3-oxazolidin-2-one

A solution of (5*R*)-3-[6-(but-3-ynyloxy)hexyl]-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (500 mg) and 2-(3-iodophenyl)-4,6-diphenyl-1,3,2-dioxaborinane (603 mg) in acetonitrile (5 ml) and triethylamine (3 ml) was treated with bis(triphenylphosphine)palladium dichloride (84 mg) and copper (I) iodide (23 mg) and the mixture was stirred under nitrogen for 4.5 h. The mixture was concentrated under reduced pressure and the residue was purified by chromatography on a Bond Elut cartridge (10 g) eluting with DCM, followed by ether to give the *title compound* (572mg). LCMS RT = 3.50min.

iv) Methyl 3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-4-carboxylate

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-[6-({4-[3-(4,6-diphenyl-1,3,2-dioxaborinan-2-yl)phenyl]but-3-ynyl}oxy)hexyl]-1,3-oxazolidin-2-one (570 mg) in ethanol (3 ml) and ethyl acetate (1 ml) was hydrogenated over 10% palladium on carbon (57 mg) over 2 days. The catalyst was removed by filtration and the filtrated was concentrated

under reduced pressure to give the saturated boronic ester (470 mg). A portion of this (200 mg) was dissolved in DMF (3 ml) and treated with methyl 4-iodobenzoate (110 mg), caesium carbonate (137 mg), and tetrakis(triphenylphosphine) palladium (0) (35 mg) and the mixture was heated to 100 °C for 1 h. The mixture was cooled and then partitioned between ether and water. The organic layer was washed with water, brine dried and chromatographed on a biotage cartridge (40 g) eluting with heptane-ether (1:2) to give the *title compound* (126 mg) LCMS RT = 4.21 min.

v) 3'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-4-carboxylic acid

Prepared using methods similar to those described in Example 1 v) LCMS RT = 2.97 min

vi) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-carboxylic acid acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.61 min, ES-ve 534(M-H)$^-$.

Example 10

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-N-isopropyl[1,1'-biphenyl]-2-sulfonamide acetate

i) 4-(4-Iodophenyl)butan-1-ol

A solution of borane-tetrahydrofuran (200ml) was added dropwise to a stirred solution of 4-(4-iodophenyl)butanoic acid (25g) at 0°C under nitrogen. After 2h methanol (200ml) was added dropwise. And then the solvent was removed *in vacuo.* The residue was partitioned between ether and water and the organic phase was separated. The combined organic layers were dried (Na_2SO_4) and evaporated to give *the title compound* (23 g). LCMS RT = 3.34 min.

ii) 1-{4-[(6-Bromohexyl)oxy]butyl}-4-iodobenzene

4-(4-Iodophenyl)butan-1-ol (22g) was stirred with 1,6-dibromohexane (61ml) and tetrabutylammonium hydrogen sulphate(1.0g) in 50% sodium hydroxide solution (300ml) for 18h. The reaction was poured into water and extracted into ether. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was

purified by chromatography on flash silica (800g) eluting with n-heptane and then heptane-ether (3:1) to give *the title compound* (12 g). LCMS RT = 4.23 min.

iii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(4-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one

Sodium hydride (60% oil dispersion, 1.4g) was added to a stirred solution of (5*R*)-(2,2-dimethyl-4*H*-1,3-benzodioxin-6yl)-1,3oxazolidin-2-one (6.0g) in dry dimethylformamide (80ml) at 0° under nitrogen. After 20 min a solution of 1-{4-[(6-bromohexyl)oxy]butyl}-4-iodobenzene (12.6g) in dry dimethylformamide (30ml) was added dropwise. The mixture was stirred for 15h at ambient temperature. The mixture was poured into an aqueous ammonium chloride solution (700ml) and extracted into ethyl acetate. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. Purification by chromatography on a biotage cartridge (90g) using ether- petroleum ether (40-60°) (4:1) gave the *title compound* as a clear oil (10g). LCMS RT = 4.19 min.

iv) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one

A stirred mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(4-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one (3.6 g), bis(pinacolato)diboron (3.6g), potassium acetate(2.2g) and 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride complex with dichloromethane (200mg) in dimethylformamide (80ml) was heated at 80° under nitrogen for 18h. The mixture was cooled and poured into water and extracted into ethyl acetate. The organic extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (90g) eluting with ether-petroleum ether (40-60°) to give *the title compound* (3.4g) LCMS RT = 4.19 min.

v) *tert*-Butyl (2-bromophenyl)sulfonyl(isopropyl)carbamate

A stirred solution of 2-bromo-benzenesulphonyl chloride (2.0g) in tetrahydrofuran (50ml) was treated with isopropylamine (5ml) at 0° for 10 min. The solvent was evaporated and the residual solid triturated under water. A portion of the compound (1.0g) in acetonitrile (20ml) was treated with di-*tert*-butyl dicarbonate (1.0g), 4-(dimethylamino)pyridine (44mg) and triethylamine (0.7ml) at 0° under nitrogen for 15 min. The solvent was evaporated and the residue was partitioned between ethyl acetate and 2M hydrochloric acid. The

organic extract was washed with water, dried (Na_2SO_4) and evaporated to give *the title compound* as a pale yellow solid (1.2g).
TLC (silica, petroleum ether-ether 4:1) R_f = 0.44

vi) *tert*-Butyl {4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-2-yl}sulfonyl(isopropyl)carbamate

A stirred mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl]butoxy}hexyl)-1,3-oxazolidin-2-one) (216 mg), *tert*-butyl (2-bromophenyl)sulfonyl(isopropyl)carbamate (160mg), potassium carbonate (20mg) and 1,1' bis(diphenylphosphino) ferrocene palladium dichloride complex with dichloromethane (50mg) in 1,2-dimethoxyethane (4ml) was heated at 85° for 4h. The mixture was cooled, diluted with water and extracted with ethyl acetate. The organic extract was washed with water, dried (Na_2SO_4) and evaporated. Purification of the residual oil by chromatography on a biotage cartridge (8g) using ether-hexane (4:1) as the eluent gave *the title compound* as a clear oil (130mg). LCMS RT = 4.36 min

vii) 4'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-*N*-isopropyl[1,1'-biphenyl]-2-sulfonamide

Prepared using methods similar to those described in Example 1 v). TLC (SiO_2) dichloromethane-ethanol-ammonia (100:8:1) R_f = 0.2

viii) 4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-*N*-isopropyl[1,1'-biphenyl]-2-sulfonamide acetate

Prepared using methods similar to those described in Example 1 vi). LCMS RT = 2.81 min, ES+ve 613 $(MH)^+$

Example 11

N-Cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

i) *tert*-Butyl (2-bromophenyl)sulfonyl(cyclopropyl)carbamate

Was prepared using methods similar to those described in example 10 v)
LCMS RT= 3.37min

ii) *tert*-Butyl cyclopropyl({3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-2-yl}sulfonyl)carbamate

Was prepared using methods similar to those described in Example 10vi) LCMS RT= 4.19min.

iii) *N*-Cyclopropyl-4'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}[1,1'-biphenyl]-2-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 3.12 min.

iv) *N*-Cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

Was prepared using methods similar to those described in Example 1 vi)
LCMS RT= 2.87min, ES+ve 612(MH^+).

Example 12

2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(morpholin-4-ylsulfonyl)[1,1'-biphenyl]-4-yl]butoxy}hexyl)amino]ethyl}phenol acetate

i) 4-[(2-Bromophenyl)sulfonyl]morpholine

Morpholine (2ml) was added to a stirred solution of 2- bromo benzenesulphonyl chloride(1.0g) in dichloromethane (20ml) at 5° under nitrogen. The solvent was evaporated and the residual solid was triturated with water to give *the title compound* (1.3g). TLC (SiO_2, ether-hexane 1:1) R_f 0.35.

ii) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[2'-(morpholin-4-ylsulfonyl)[1,1'-biphenyl]-4-yl]butoxy}hexyl)-1,3-oxazolidin-2-one

Was prepared using methods similar to those described in Example 10 vi) LCMS RT= 3.96 min.

iii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(6-{4-[2'-(morpholin-4-ylsulfonyl)[1,1'-biphenyl]-4-yl]butoxy}hexyl)amino]ethanol

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 3.08 min.

iv) 2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(morpholin-4-ylsulfonyl)[1,1'-biphenyl]-4-yl]butoxy}hexyl)amino]ethyl}phenol acetate

Was prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.95 min, ES+ve 641 $(MH)^+$.

Example 13

N-Ethyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-*N*-methyl[1,1'-biphenyl]-2-sulfonamide acetate

i) 2-Bromo-*N*-ethyl-*N*-methylbenzenesulfonamide

Was prepared using methods similar to those described in Example 12 i) LCMS RT= 3.04 min

ii) 4'-[4-({6-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-*N*-ethyl-*N*-methyl[1,1'-biphenyl]-2-sulfonamide

Was prepared using methods similar to those described in Example 10 vi) LCMS RT= 4.08 min.

iii) 4'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-*N*-ethyl-*N*-methyl[1,1'-biphenyl]-2-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 3.29 min.

iv) *N*-Ethyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-*N*-methyl[1,1'-biphenyl]-2-sulfonamide acetate

Was prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.93 min, ES+ve $(MH)^+$.

Example 14

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

i) *tert*-Butyl (2-bromophenyl)sulfonylcarbamate

Ammonia (50ml) was added to a stirred solution of 2-bromo benzenesulphonyl chloride (5.0g) in tetrahydrofuran (100ml) at 5°C. The mixture was stirred for 20 min and then evaporated to dryness and then the residual solid was triturated with water. The solid was collected by filtration and suspended in dichloromethane (100ml). 4-(Dimethylamino)pyridine (0.25 g) and triethylamine (3.2ml) were added, followed by di-*tert*-butyl dicarbonate (5.8 g) and the solution was stirred at ambient temperature for 1h. The solution was washed with 1M hydrochloric acid, water and dried (Na_2SO_4). The solvent was evaporated to give *the title compound* (5.8g). LCMS RT = 3.08 min.

ii) *tert*-Butyl (2-bromophenyl)sulfonyl{[2-(trimethylsilyl)ethoxy]methyl}carbamate

Sodium hydride (60% dispersion in oil, 252 mg) was added to a stirred solution of *tert*-butyl (2-bromophenyl)sulfonylcarbamate (2.0 g) in dry dimethylformamide (20ml) at 5° under nitrogen. After 15min 2-(trimethylsilyl)ethoxymethyl chloride (2 ml) was added and the mixture was stirred for 30 min at 5°. The mixture was poured into an aqueous ammonium chloride solution and extracted into ether. The organic extract was washed with water, dried (Na_2SO_4) and evaporated to give *the title compound* as a clear oil (2.4 g). LCMS RT = 3.99 min.

iii) *tert*-Butyl {4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-2-yl}sulfonyl{[2-(trimethylsilyl)ethoxy]methyl}carbamate

Was prepared using methods similar to those described in Example10 vi) LCMS RT = 4.46 min

i) 4'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}[1,1'-biphenyl]-2-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS = 2.80 min.

ii) 4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

Was prepared using methods similar to those described in Example 1vi) LCMS = 2.57 min, ES+ve 571 $(MH)^+$.

Example 15

4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide acetate

i) 4-(Tributylstannyl)benzenesulfonamide

A stirred mixture of 4-iodobenzenesulfonamide (8.33 g), hexabutylditin (20.5g) and tetrakis(triphenylphosphine) palladium (0) (200mg) in dioxan (80ml) and toluene (70ml) was heated at reflux for 18 h. The mixture was absorbed onto silica gel (merck 9385) and purified by flash chromatography (200g) eluting with cyclohexane-ethyl acetate (3:1). The appropriate fractions were evaporated to give *the title compound* as a clear oil (6.95g). LCMS RT = 4.34 min.

ii) 4'-[4-({6-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-4-sulfonamide

A stirred mixture of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(4-iodophenyl)butoxy]hexyl}-1,3-oxazolidin-2-one(225mg), 4-(tributylstannyl) benzenesulfonamide (250mg) and silver oxide (86mg) with [1,4-bis(diphenylphosphino)butane]palladium dichloride in dioxan (5ml) was heated at 85° for 18h. The reaction mixture was filtered through celite and washed with ethyl acetate. The filtrate was evaporated to dryness and the residual oil was purified by chromatography on a biotage cartridge (8g) eluting with ether. The appropriate fractions were evaporated to give *the title compound* as a clear oil (60mg). LCMS RT = 4.01 min.

iii) 4'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}[1,1'-biphenyl]-4-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 2.96 min.

iv) 4'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide acetate
Was prepared using methods similar to those described in Example1 vi) LCMS RT=2.72 min, ES+ve 571 $(MH)^+$.

Example 16

N-Cyclopropyl-3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide

i) *tert*-Butyl cyclopropyl({3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-2-yl}sulfonyl)carbamate
Prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.12 min.

ii) *N*-Cyclopropyl-3'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}[1,1'-biphenyl]-2-sulfonamide
Prepared using methods similar to those described in Example 1 v) TLC [SiO_2, dichloromethane – ethanol -0.88 ammonia (100:8:1)], R_f 0.27

iii) *N*-Cyclopropyl-3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide
Was prepared using methods similar to those described in Example1 vi) LCMS RT = 2.75 min, ES+ve 611 $(MH)^+$.

Example 17

3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

i) *tert*-Butyl {3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-2-yl}sulfonyl{[2-(trimethylsilyl)ethoxy]methyl}carbamate
Was prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.47 min.

ii) 3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-2-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 2.80 min.

iii) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-2-sulfonamide acetate

Was prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.56 min, ES+ve 571 $(MH)^+$.

Example 18

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide

i) 3'-[4-({6-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl][1,1'-biphenyl]-4-sulfonamide

Was prepared using methods similar to those described in Example 10 vi) LCMS RT = 3.89 min.

ii) 3'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}[1,1'-biphenyl]-4-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 3.05 min.

iii) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)[1,1'-biphenyl]-4-sulfonamide acetate

Was prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.76 min, ES+ve 571 (MH^+)

Example 19

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-sulfonamide acetate

i) *tert*-Butyl {3'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-yl}sulfonyl{[2-(trimethylsilyl)ethoxy]methyl}carbamate

Was prepared using methods similar to those described in Example 17 i) LCMS RT = 4.76 min

ii) 3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-sulfonamide

Was prepared using methods similar to those described in Example 1 v) LCMS RT = 3.29 min

iii) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-sulfonamide acetate

Was prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.50 min, ES+ve 571 $(MH)^+$.

Example 20

N-[3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]urea acetate

i) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3'-nitro-1,1'-biphenyl-3-yl)butoxy]hexyl}-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.25 min.

ii) (5*R*)-3-{6-[4-(3'-Amino-1,1'-biphenyl-3-yl)butoxy]hexyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

A solution of (5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-{6-[4-(3'-nitro-1,1'-biphenyl-3-yl)butoxy]hexyl}-1,3-oxazolidin-2-one (0.38 g) in ethanol (20ml) and ethyl acetate (20ml) was hydrogenated at room temperature and pressure in the presence of platinum oxide (50 mg) for 1 h. The catalyst was removed by filtration through celite and the filtrate evaporated to dryness to give *the title compound* as a clear oil (0.29 g). LCMS RT = 4.08 min.

iii) *N*-{3'-[4-({6-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-3-yl}urea

Sodium cyanate (39 mg) was added to a stirred solution of (5*R*)-3-{6-[4-(3'-amino-1,1'-biphenyl-3-yl)butoxy]hexyl}-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one (0.38g) in glacial acetic acid (2 ml) and water (2 ml) at room temperature. After 20 min

the solution was poured into a phosphate buffer solution (pH 5, 25 ml) and extracted into dichloromethane. The extracts were dried and evaporated to give *the title compound* (160 mg). LCMS RT = 3.98 min.

iv) *N*-(3'-{4-[(6-{[(2*R*)-2-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-3-yl)urea

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.25 min.

v) *N*-[3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-yl]urea acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.51 min, ES+ve 550 (MH^+).

Example 21

N-cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxamide

i) Methyl 4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxylate

Prepared using methods similar to those described in Example 10 vi

TLC [SiO_2, diethylether-Heptane (4:1)], R_f 0.33.

ii) 4'-[4-({6-[(5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxylic acid

A stirred mixture of methyl 4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxylate (93 mg) in methanol (1ml) and 2M sodium hydroxide solution (1ml) was heated at 80°C for 45 min. The mixture was cooled, poured into a phosphate buffer solution (pH 5) and extracted into ethyl acetate. The extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (4g) eluting with ether. The appropriate fractions were evaporated to give *the title compound* as a clear oil (62 mg)

TLC (SiO_2, diethylether) R_f 0.28.

iii) *N*-cyclopropyl-4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxamide

A stirred mixture of 4'-[4-({6-[(5*R*)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-oxo-1,3-oxazolidin-3-yl]hexyl}oxy)butyl]-1,1'-biphenyl-2-carboxylic acid (126 mg), 1-[3-(dimethylamino)propyl]-3-ethyl carbodiimide hydrochloride (0.048g), 1-hydroxybenzotriazole (0.028g), triethylamine (0.67ml) and cyclopropylamine (0.067g) in dichloromethane (3ml) was left for 18 h. The mixture was then partitioned between dichloromethane and water. The organic extracts were dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (4g) eluting with ether-hexane (4:1). The fractions were evaporated to give *the title compound* as a clear oil (0.07g) LCMS RT = 3.79 min.

iv) *N*-cyclopropyl-4'-{4-[(6-{[(2*R*)-2-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-hydroxyethyl]amino}hexyl)oxy]butyl}-1,1'-biphenyl-2-carboxamide

Prepared using similar methods to those described in Example 1 v) TLC [SiO_2, dichloromethane - ethanol -0.88 ammonia (100:8:1)] R_f 0.42.

v) *N*-cyclopropyl-4'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-carboxamide

Prepared using methods similar to those described in Example 1 vi LCMS RT = 2.68 min, ES+ve 575 (MH^+).

Example 22

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-ol acetate

i) (5*R*)-3-(6-{4-[3'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 10 vi LCMS RT = 4.41 min.

ii) (1R)-2-[(6-{4-[3'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4H-1,3-benzodioxin-6-yl)ethanol

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.65 min.

iii) 4-{(1*R*)-2-[(6-{4-[3'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 3.41min.

iv) 3'-(4-{[6-({(2*R*)-2-hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-3-ol acetate

A solution of 4-{(1*R*)-2-[(6-{4-[3'-(benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate (41 mg) in ethanol (5ml) was hydrogenated over 10% palladium on carbon (15 mg) for 1h at room temperature. The catalyst was removed by filtration through celite and the filtrate evaporated to dryness to give *the title compound* as a clear oil (31 mg). LCMS RT = 2.95 min, ES+ve 508 (MH^+).

Example 23

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-ol acetate

i) (5*R*)-3-(6-{4-[2'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.30 min.

ii) 4-{(1*R*)-2-[(6-{4-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

Prepared using methods similar to those described in Example 1 v) LCMS RT = 3.26 min.

iii) 4-{(1*R*)-2-[(6-{4-[2'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 3.07 min.

iv) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-2-ol acetate

Prepared using methods similar to those described in Example 22 iv) LCMS RT = 2.78 min, ES+ve 508 (MH^+).

Example 24

3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-ol acetate

i) (5*R*)-3-(6-{4-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)-5-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.35 min.

ii) (1*R*)-2-[(6-{4-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-(2,2-dimethyl-4*H*-1,3-benzodioxin-6-yl)ethanol

Prepared using methods similar to those described in Example 1 v)
LCMS RT = 3.61 min.

iii) 4-{(1*R*)-2-[(6-{4-[4'-(Benzyloxy)-1,1'-biphenyl-3-yl]butoxy}hexyl)amino]-1-hydroxyethyl}-2-(hydroxymethyl)phenol

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 3.15 min.

iv) 3'-(4-{[6-({(2*R*)-2-Hydroxy-2-[4-hydroxy-3-(hydroxymethyl)phenyl]ethyl}amino)hexyl]oxy}butyl)-1,1'-biphenyl-4-ol acetate

Prepared using methods similar to those described in Example 22 iv
LCMS RT = 2.78, ES+ve 508 (MH^+).

Example 25

2-(hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(1*H*-tetraazol-5-yl)-1,1'-biphenyl-4-yl]butoxy}hexyl)amino]ethyl}phenol acetate

i) (5*R*)-5-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-3-(6-{4-[2'-(1-trityl-1*H*-tetraazol-5-yl)-1,1'-biphenyl-4-yl]butoxy}hexyl)-1,3-oxazolidin-2-one

Prepared using methods similar to those described in Example 10 vi) LCMS RT = 4.56 min.

ii) (1*R*)-1-(2,2-Dimethyl-4*H*-1,3-benzodioxin-6-yl)-2-[(6-{4-[2'-(1-trityl-1*H*-tetraazol-5-yl)-1,1'-biphenyl-4-yl]butoxy}hexyl)amino]ethanol

Prepared using methods similar to those described in Example 1 v) TLC (SiO_2) R_f 0.26 dichloromethane-ethanol- 0.88 ammonia (100:8:1).

iii) 2-(Hydroxymethyl)-4-{(1*R*)-1-hydroxy-2-[(6-{4-[2'-(1*H*-tetraazol-5-yl)-1,1'-biphenyl-4-yl]butoxy}hexyl)amino]ethyl}phenol acetate

Prepared using methods similar to those described in Example 1 vi) LCMS RT = 2.70 min, ES+ve 560 (MH^+).

Example 26

2-Hydroxy-5-[(1*R*)-1-hydroxy-2-({6-[4-(3'-hydroxy-1,1'-biphenyl-3-yl)butoxy]hexyl}amino)ethyl]phenylformamide with (2*E*)-but-2-enedioic acid (1:1)

i) 2-(Benzyloxy)-5-{(1*R*)-1-(benzyloxy)-2-[(6-{[4-(3'-bromo-1,1'-biphenyl-3-yl)but-3-ynyl]oxy}hexyl)amino]ethyl}phenylformamide

A stirred solution of 5-((1*R*)-2-{benzyl[6-(but-3-ynyloxy)hexyl]amino}-1-hydroxyethyl)-2-(benzyloxy)phenylformamide (WO02/076933, 562 mg) 3-bromo-1-iodobenzene (435 mg), cuprous iodide (0.1g) and 1,1 bis(triphenylphosphine) palladium dichloride (0.1g) in DMF (10ml) and triethylamine (10ml) was left for 2 days at room temperature. The mixture was poured into water and extracted into ethyl acetate. The combined organic extracts were dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (40g) eluting with ether-ethyl acetate (9:1). The appropriate fractions were evaporated to give *the title compound* (274 mg). LCMS RT = 3.43 min.

ii) 2-(Benzyloxy)-5-((1*R*)-1-(benzyloxy)-2-{[6-({4-[3'-(benzyloxy)-1,1'-biphenyl-3-yl]but-3-ynyl}oxy)hexyl]amino}ethyl)phenylformamide

A stirred solution of 2-(benzyloxy)-5-{(1*R*)-1-(benzyloxy)-2-[(6-{[4-(3'-bromo-1,1'-biphenyl-3-yl)but-3-ynyl]oxy}hexyl)amino]ethyl}phenylformamide (0.27g), 3-(benzyloxy)phenylboronic acid (130 mg) and tetrakis(triphenylphosphine) palladium (0) (50 mg) in 1,2-dimethoxymethane (10 ml) and 1M sodium carbonate solution (5 ml) was heated at 90 °C for 4 h. The mixture was poured into water and extracted into ethyl acetate. The combined extracts were washed with water, dried (Na_2SO_4) and evaporated. The residual oil was purified by chromatography on a biotage cartridge (40g) eluting with dichloromethane-ethanol–0.88 ammonia (100:8:1). The appropriate fractions were evaporated to give the *title compound* (0.15g). LCMS RT = 3.70 min.

iii) 2-Hydroxy-5-[(1*R*)-1-hydroxy-2-({6-[4-(3'-hydroxy-1,1'-biphenyl-3-yl)butoxy]hexyl}amino)ethyl]phenylformamide with (2*E*)-but-2-enedioic acid (1:1)

A stirred solution of 2-(benzyloxy)-5-((1*R*)-1-(benzyloxy)-2-{[6-({4-[3'-(benzyloxy)-1,1'-biphenyl-3-yl]but-3-ynyl}oxy)hexyl]amino}ethyl)phenylformamide (0.15g) in ethanol (10ml)

and ethyl acetate (5ml) was hydrogenated over 10% palladium on carbon (0.03g) and palladium hydroxide on carbon (0.06g) for 18 h at 100 p.s.i. The catalysts were removed by filtration through celite and the filtrate was evaporated to dryness. The residual oil was purified by chromatography on a biotage cartridge (4g) eluting with dichloromethane-ethanol-0.88 ammonia (50:8:1). The appropriate fractions were evaporated and the residual oil was dissolved in methanol (10ml) and treated with fumaric acid (0.5 equivalents) and evaporated to dryness to give the *title compound* (0.027g). LCMS RT = 2.92 min, ES+ve 521 (MH^+).

BIOLOGICAL ACTIVITY

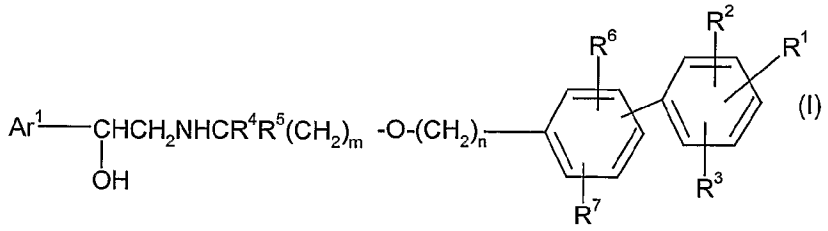
The potencies of the aforementioned compounds were determined using frog melanophores transfected with the human beta 2 adrenoreceptor. The cells were incubated with melatonin to induce pigment aggregation. Pigment dispersal was induced by compounds acting on the human beta 2 adrenoreceptor. The beta 2 agonist activity of test compounds was assessed by their ability to induce a change in light transmittance across a melanophore monolayer (a consequence of pigment dispersal). At the human beta 2 adrenoreceptor, compounds of examples 1-26 had IC_{50} values below 1 μM.

Potency at other beta adrenoreceptor subtypes was determined using chinese hamster ovary cells transfected with either the human beta 1 adrenoreceptor or the human beta 3 adrenoreceptor. Agonist activity was assessed by measuring changes in intracellular cyclic AMP.

The application of which this description and claims forms part may be used as a basis for priority in respect of any subsequent application. The claims of such subsequent application may be directed to any feature or combination of features described herein. They may take the form of product, composition, process, or use claims and may include, by way of example and without limitation, the following claims:

CLAIMS

1. A compound of formula (I):



(I)

or a salt, solvate, or physiologically functional derivative thereof, wherein:

m is an integer of from 2 to 8;
n is an integer of from 3 to 7;
with the proviso that m + n is 5 to 12;

R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8C(O)NC(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or $-XC(O)NR^9R^{10}$;

or R^1 is selected from -X-aryl, -X-hetaryl, or -X-(aryloxy), each optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, C_{1-6}haloalkyl, cyano, nitro, $CONR^9R^{10}$, $-NR^8C(O)R^9$, SR^8, SOR^8, $-SO_2R^8$, $-SO_2NR^9R^{10}$, $-CO_2R^{10}$, $-NR^9R^{10}$, or hetaryl optionally substituted by 1 or 2 groups independently selected from hydroxy, C_{1-6}alkoxy, halo, C_{1-6}alkyl, or C_{1-6}haloalkyl;

X is $-(CH_2)_r-$ or C_{2-6} alkenylene;

r is an integer from 0 to 6;

R^8 and R^9 are independently selected from hydrogen, C_{1-6}alkyl, C_{3-7}cycloalkyl, aryl, hetaryl, hetaryl(C_{1-6}alkyl)- and aryl(C_{1-6}alkyl)- and R^8 and R^9 are each independently optionally substituted by 1 or 2 groups independently selected from halo, C_{1-6}alkyl,

C_{3-7} cycloalkyl, C_{1-6} alkoxy, C_{1-6}haloalkyl, -NHC(O)(C_{1-5}alkyl), -SO_2(C_{1-6}alkyl), -SO_2(aryl), -CO_2H, and -CO_2(C_{1-4}alkyl), -NH_2, -NH(C_{1-6}alkyl), aryl(C_{1-6}alkyl)-, aryl(C_{2-6}alkenyl)-, aryl(C_{2-6}alkynyl)-, hetaryl(C_{1-6}alkyl)-, -$NHSO_2$aryl, -NH(hetarylC_{1-6}alkyl), -$NHSO_2$hetaryl, -$NHSO_2$(C_{1-6}alkyl), -NHC(O)aryl, or -NHC(O)hetaryl:

or where R^1 is –$XNR^8C(O)NR^9R^{10}$, R^8 and R^9 may, together with the -NC(O)N- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring;

or where R^1 is –$XNR^8C(O)OR^9$, R^8 and R^9 may, together with the -NC(O)O- portion of the group R^1 to which they are bonded, form a saturated or unsaturated ring;

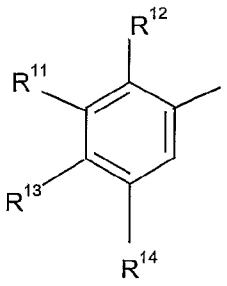
R^{10} is selected from hydrogen, C_{1-6}alkyl and C_{3-7} cycloalkyl;

or where R^1 contains a moiety –NR^9R^{10} or R^9 and R^{10} may, together with the nitrogen to which they are bonded, form a 5-, 6-, or 7- membered nitrogen containing ring;

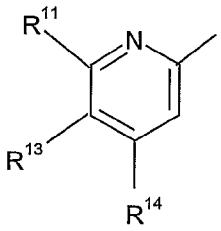
R^2, R^3, R^6, and $R^7$are independently selected from hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halo, and C_{1-4} haloalkyl;

R^4 and R^5 are independently selected from hydrogen and C_{1-4} alkyl with the proviso that the total number of carbon atoms in R^4 and R^5 is not more than 4.

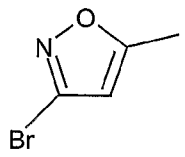
Ar^1 is a group selected from



(a)

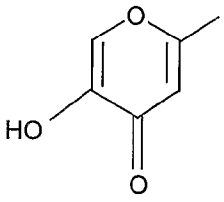


(b)



(c)

and



(d)

wherein R^{11} represents hydrogen, halogen, $-(CH_2)_qOR^{15}$, $-NR^{15}C(O)R^{16}$, $-NR^{15}SO_2R^{16}$, $-SO_2NR^{15}R^{16}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$,
and R^{12} represents hydrogen, halogen or C_{1-4} alkyl;

or R^{11} represents $-NHR^{18}$ and R^{12} and $-NHR^{18}$ together form a 5- or 6- membered heterocyclic ring;

R^{13} represents hydrogen, halogen, $-OR^{15}$ or $-NR^{15}R^{16}$;

R^{14} represents hydrogen, halogen, haloC_{1-4} alkyl, $-OR^{15}$, $-NR^{15}R^{16}$, $-OC(O)R^{17}$ or $OC(O)NR^{15}R^{16}$;

R^{15} and R^{16} each independently represents hydrogen or C_{1-4} alkyl, or in the groups $-NR^{15}R^{16}$, $-SO_2NR^{15}R^{16}$ and $-OC(O)NR^{15}R^{16}$, R^{15} and R^{16} independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached form a 5-, 6- or 7- membered nitrogen-containing ring,

R^{17} represents an aryl (eg phenyl or naphthyl) group which may be unsubstituted or substituted by one or more substituents selected from halogen, C_{1-4} alkyl,

hydroxy, C_{1-4} alkoxy or halo C_{1-4} alkyl; and

q is zero or an integer from 1 to 4.

2. A compound of formula (I) as defined in claim 1, or a salt, solvate or physiologically functional derivative thereof, wherein R^1 is selected from hydrogen, C_{1-6}alkyl, hydroxy, C_{1-6} alkoxy, cyano, nitro, halo, C_{1-6}haloalkyl, $-XNR^8C(O)R^9$, $-XNR^8C(O)NR^9R^{10}$, $-XNR^8C(O)NC(O)NR^9R^{10}$, $-XNR^8SO_2R^9$, $-XSO_2NR^9R^{10}$, XSR^8, $XSOR^8$, XSO_2R^8, $-XNR^9R^{10}$, $-XNR^8C(O)OR^9$, $XNR^8SO_2NR^9R^{10}$, XCO_2R^{10}, or $-XC(O)NR^9R^{10}$;
R^{11} is as defined above except that R^{11} is not hydrogen; and
all other substituents are as defined for formula (I) above.

3. A compound according to claim 1 or claim 2 wherein R^1 represents hydroxy, $-XR^8(CO)NR^9R^{10}$, $-XSO_2NR^9R^{10}$, $-XCO_2R^{10}$, $XC(O)NR^9R^{10}$ or X-hetaryl.

4. A compound according to any of claims 1 to 3 wherein R^2 and R^3 each represent hydrogen.

5. A compound according to any of claims 1 to 4 wherein R^4 and R^5 are independently selected from hydrogen and methyl.

6. A compound according to any of claims 1 to 5 wherein R^6 and R^7 are independently selected from hydrogen and methyl.

7. A compound according to any of claims 1 to 6 wherein m is suitably 3, 4, 5 or 6 and n is suitable 3, 4, 5 or 6.

8. A compound of formula (I) wherein Ar^1 is a group of structure (a) or (b) as defined in claim 1.

9. A method for the prophylaxis or treatment of a clinical condition in a mammal, such as a human, for which a selective β_2-adrenoreceptor agonist is indicated, which comprises administration of a therapeutically effective amount of a compound of formula (I) according to any of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof.

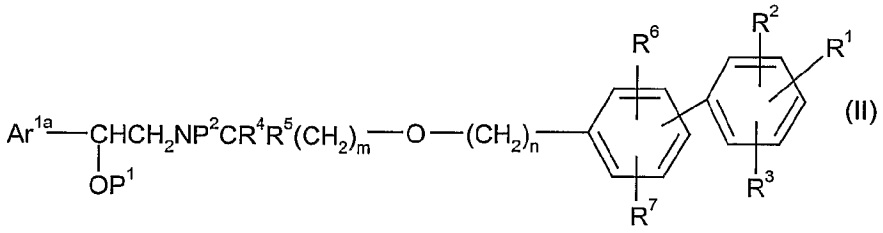
10. A compound of formula (I) according to any of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof for use in medical therapy.

11. A pharmaceutical formulation comprising a compound of formula (I) according to any of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof, and a pharmaceutically acceptable carrier or excipient, and optionally one or more other therapeutic ingredients.

12. The use of a compound of formula (I) according to any of claims 1 to 8, or a pharmaceutically acceptable salt, solvate, or physiologically functional derivative thereof in the manufacture of a medicament for the prophylaxis or treatment of a clinical condition for which a selective β_2-adrenoreceptor agonist is indicated.

13. A process for the preparation of a compound of formula (I), according to any of claims 1 to 8, or a salt, solvate, or physiologically functional derivative thereof, which comprises:

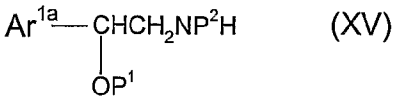
(a) deprotection of a protected intermediate, for example of formula (II).



(II)

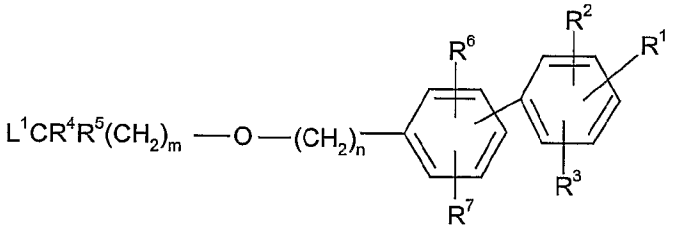
or a salt or solvate thereof, wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7, m, and n are as defined for the compound of formula (I), Ar^{1a} represents an optionally protected form of Ar^1; and P^1 and P^2 are each independently either hydrogen or a protecting group, provided that the compound of formula (II) contains at least one protecting group;

(b) alkylation of an amine of formula (XV):



(XV)

wherein Ar^{1a}, P^1 and P^2 are as defined for formula (II);
with a compound of formula (XIV):



(XIV)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^7 m and n are as defined for formula (II) and L^1 is as defined for formula (VIII);

followed by the following steps in any order:

(i) optional removal of any protecting groups;

(ii) optional separation of an enantiomer from a mixture of enantiomers;

(iii) optional conversion of the product to a corresponding salt, solvate, or physiologically functional derivative thereof.

14. A compound of formula (II), (III) or (IV) as defined hereinabove.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12194

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07C217/10 C07C275/32 C07C311/29 C07D263/22 C07D413/04
A61K31/137 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07C C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 230 525 A (GLAXO GROUP LTD) 24 October 1990 (1990-10-24) claims	1-14
A	GB 2 140 800 A (GLAXO GROUP LTD) 5 December 1984 (1984-12-05) cited in the application claims	1-14

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
3 February 2004	18/02/2004

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	CHOULY, J

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/12194

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 9 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/12194

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB 2230525 A	24-10-1990	NONE	
GB 2140800 A	05-12-1984	AT 390611 B	11-06-1990
		AT 129184 A	15-11-1989
		AU 573212 B2	02-06-1988
		AU 2706484 A	25-10-1984
		BE 899448 A1	18-10-1984
		BE 900835 A4	17-04-1985
		BG 61490 B2	30-09-1997
		CA 1335999 C	20-06-1995
		CA 1336004 C	20-06-1995
		CH 661497 A5	31-07-1987
		CH 667084 A5	15-09-1988
		CZ 9104028 A3	12-05-1993
		CY 1482 A	08-12-1989
		CZ 285602 B6	15-09-1999
		DE 3414752 A1	18-10-1984
		DE 3448338 C2	19-05-1993
		DE 3448452 C2	05-01-1994
		DK 158092 A	30-12-1992
		DK 201784 A	19-10-1984
		ES 8505641 A1	01-10-1985
		ES 8609209 A1	16-12-1986
		FI 841548 A ,B,	19-10-1984
		FR 2545482 A1	09-11-1984
		GB 2176476 A ,B	31-12-1986
		GR 79925 A1	31-10-1984
		HK 36889 A	12-05-1989
		HU 200160 B	28-04-1990
		IE 57237 B1	17-06-1992
		IL 71569 A	30-10-1987
		IT 1199112 B	30-12-1988
		JP 1862136 C	08-08-1994
		JP 5069817 B	01-10-1993
		JP 63264443 A	01-11-1988
		JP 1643826 C	28-02-1992
		JP 3000858 B	09-01-1991
		JP 59199659 A	12-11-1984
		JP 2001385 C	20-12-1995
		JP 6087800 A	29-03-1994
		JP 7029997 B	05-04-1995
		KE 3864 A	19-05-1989
		KR 9204186 B1	30-05-1992
		LU 85329 A1	04-06-1985
		LU 88265 A9	03-02-1994
		MX 9203226 A1	01-07-1992
		NL 8401258 A ,B,	16-11-1984
		NO 841568 A ,B,	19-10-1984
		NZ 207885 A	29-11-1988
		NZ 221999 A	29-11-1988
		PH 21574 A	11-12-1987
		PT 78443 A ,B	01-05-1984